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The Effects of a Multiple-Modality Mind-Motor Program on Vascular Outcomes in Community-Dwelling Older Adults with Subjective Cognitive Complaints

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A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

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(Thesis format: Monograph Article)

by

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Abstract

Studies have found a link between cardiovascular risk factors (CVRFs) and Alzheimer's disease however; the mechanism by which CVRFs increase the risk of cognitive decline is not fully understood. The current study attempts to improve CVRFs in order to enhance cognition in older adults. Primary outcomes include ambulatory and clinical resting systolic and diastolic blood pressure (SBP; DBP). In total, 89 community-dwelling older adults with subjective cognitive complaints were randomized to either a multiple-modality mind-motor (M4) exercise or a multiple-modality (M2) exercise only. Significance was found in nighttime peak SBP (6.55 mmHg, p=.04) between groups, with a decrease in M2 compared to M4. Clinical resting SBP also decreased (6.99 mmHg, p=.03) between groups, whereby M4 further decreased compared to M2. Both M2 and M4 have some influence on ambulatory and clinical resting BP however, further research is required to elicit the effects of M4 and M2 on CVRFs.

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Abbreviations

ABPM	ambulatory blood pressure monitor
AC	arterial compliance
AD	Alzheimer's Disease
AE	aerobic exercise
BMI	body mass index
BP	blood pressure
CAC	carotid arterial compliance
CBF	cerebral blood flow
CBS	Cambridge Brain Sciences
cDBP	clinical resting diastolic blood pressure
cSBP	clinical resting systolic blood pressure
CT	cognitive training
CV	cardiovascular
CVD	Cardiovascular Disease
CVRFs	cardiovascular risk factors
Dbbpk	peak diastolic blood pressure
DBP	diastolic blood pressure
ECG	electrocardiogram
HR	heart rate
IMT	intima-media thickness
M2	multiple modality
M2-OE	multiple modality-older elderly
M2-YE	multiple modality-younger elderly
M4	multiple modality mind-motor
M4-OE	multiple modality mind-motor-older elderly
M4-YE	multiple modality mind-motor-younger elder
MAP	mean arterial pressure
MCI	mild cognitive impairment
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
OE	older elderly
Pavg	average pulse wave velocity
Pdv	diastolic pulse wave velocity
Pedv	end-diastolic pulse wave velocity
Psv	systolic pulse wave velocity
RCT	randomized controlled trial
Sbppk	peak systolic blood pressure
SBP	systolic blood pressure
SNS	sympathetic nervous system
SSE	square stepping exercise
VO2max	maximum volume of oxygen uptake
WHO	World Health Organization
x24DBP	24-hour diastolic blood pressure
x24SBP	24-hour systolic blood pressure
YE	younger elderly

Chapter 1 : Introduction

Brief Introduction to Thesis

Cognition is referred to as the mental act or process by which knowledge is developed through the incorporation of perception, intuition, reasoning and judgement. According to Hendrie et al., cognitive health, much like physical health (i.e. vascular health), can be viewed along a continuum; ranging from optimal functioning to mild cognitive impairment to severe dementia such as Alzheimer's disease[1]. As the population continues to age, the prevalence of age-related diseases such as Cardiovascular Disease (CVD) and dementia are increasing[2]. There is growing support associated with the significance of cardiovascular risk factors (CVRFs) and the advancement of dementia, including Alzheimer's disease (AD)[2].

Increased blood pressure, along with the associated stiffening of arteries are some CVRFs that reduce cerebrovascular vasoreactivity and cerebral blood flow and render older adults to a greater risk of decreased blood flow in the brain[3,4], and poorer cognitive function. Sustained hypertension is also coupled with the formation of white matter lesions[5,6], hippocampal atrophy[7], the occurrence of neurotropic markers of AD[8] and clinical dementia[8,9]. Furthermore, age and sex also impact CV health. The Framingham Heart Study, a longitudinal study which followed participants for 40 years found a continuous increase in systolic blood pressure (SBP) between the ages of 30 and 84 years. Diastolic blood pressure (DBP) has greater variability in ageing with an increase up to the late 50's and then a decrease from the age 60 to 84 years of age. This variance in BP creates a steep incline in pulse pressure with ageing[10,11]. Sex, specifically females have a greater susceptibility to CVD in ageing[12]. Ford et al., explained the longer life expectancy within females comprises a greater fraction of the older adult population where CVD is most prevalent[12]. Therefore, both age and sex may influence CV health and lifestyle modifications should be done in order to control the risk of CVD and its associated risk factors.

Aerobic exercise (AE) has shown to overturn elevated central arterial stiffness in healthy middle-aged and older subjects[9] by enhancing blood flow in the brain's pre-frontal cortex, while resistance training can augment hippocampal volume and circulating neural growth factors, which are all proposed mechanisms that protect or improve cognition as we age[13]. For instance, a review by Lange-Asschenfeldt & Kojda concluded that exercise training reduces vascular oxidative stress and improves vascular endothelial function, both of which promote greater arterial compliance and cerebral blood flow[14]. Since decreased arterial compliance has been related to increased cerebrovascular resistance[15], and reduced cerebrovascular resistance has been observed during antihypertensive therapy[16], the use of AE to reverse hypertension (i.e., reduced arterial stiffness) may be a method to improve cognition in at-risk patients for cognitive decline who have CVD.

Observational studies have revealed physical activity as a primary method to improve vascular health, cognitive function and delay or prevent the onset of dementia[17-21]. It has also been suggested that a multiple modality (M2), (combined AE, resistance and stretching exercises) have optimal effect on cognition when compared to providing each type independent of one another[22-24]. In addition, cognitive training (CT) has also shown improved cognition, which is gaining more attention. Observational studies have found

CT to be just as effective at improving cognition as administering AE for older adults at risk of cognitive decline[25]. The exploration of a collective physical and cognitive exercise program is critical for the advancement of understanding by which different domains of exercise can impart cognitive benefits in aging[25].

There are very few randomized controlled trials that have investigated the effects of modifying vascular risk factors on cognitive health and functioning in either healthy older adults, or those with a cognitive complaint, mild cognitive impairment (MCI), or dementia[13] through the incorporation of CT. Therefore, a systematic review was conducted to establish the state of the literature available regarding the effects of CT with or without exercise on cardiovascular (CV) health in older adults and to see whether a specific program of CT and/or exercise warrants prescription for older adults at risk for future cognitive decline[26] through the improvement of CVRFs.

Chapter 2: Systematic Review

The effect of cognitive training (CT) on cardiovascular health in community-dwelling older adults: A systematic review

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KEY WORDS: cognitive training, vascular risk factors, aging, community-dwelling adults, systematic review

BACKGROUND: Exercise training may mitigate the impact of vascular risk factors on cognitive function in older adults; however, whether cognitive training can modify vascular risk factors is unclear.

OBJECTIVE: To systematically review the impact of cognitive training on vascular health in community-dwelling older adults.

Data Sources: A systematic review of English articles from year 2000 and onwards using CINAHL, Pub Med, PsycINFO, Scopus, EMBASE databases.

STUDY SELECTION: Only clinical trials (RCTs or nonrandomized studies) that assessed the effects of CT, administered with or without an exercise or physical activity component. Studies were eligible for inclusion if they studied the effectiveness of CT among healthy or cognitively impaired community-dwelling older adults aged 55 years or older.

DATA EXTRACTION: One author independently selected the trials, and two authors assessed trial quality and extracted necessary data.

OUTCOMES: The primary outcome of interest was: systolic blood pressure. Secondary outcomes included: diastolic blood pressure, lipids, inflammatory markers (i.e. Brain derived neurotrophic factor, BDNF; Insulin-like growth factor 1, IGF-1), vascular mechanics (i.e. arterial stiffness, intima-media thickness, dispensability), heart rate variability and maximum oxygen uptake (Vo2max)] or any other vascular risk factors associated with dementia (i.e. cerebral blood flow).

RESULTS: Four articles were included for qualitative synthesis. Each study reported on at least one vascular outcome. One study showed a significant increase in regional cerebral blood flow (43.6 to 59.2 ml/100·g tissue/min) and another article demonstrated a significant improvement in clinical systolic (140.06 to 128.97 mmHg) and diastolic (76.41 to 73.41 mmHg) blood pressure. However, the remaining two articles that looked at VO2max, revealed controversial results.

CONCLUSIONS Although limited studies have shown noteworthy improvement following CT in some areas of vascular health (i.e. cerebral blood flow, blood pressure and VO2max), more research is needed to confirm and include a greater number of outcomes in cardiovascular health.

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INTRODUCTION

The incidence of age-related diseases such as cardiovascular disease (CVD) and dementia are expected to significantly increase as the population ages[27]. Canada's aging population, combined with alarming trends in cardiovascular risk factors (CVRFs) such as obesity, physical inactivity, hypertension, and diabetes are expected to further increase the risk of dementia including Alzheimer’s disease (AD)[27-29].

The World Health Organization (WHO) has estimated by 2030, more than 23 million people will die annually from CVD[30]. In 2008, nearly 14 million deaths occurred after the age of 60 and more than 3 million deaths occurred before the age of 60[30]. The WHO has also projected that the total number of people with dementia will almost double every 20 years to 65.7 million in 2030 and 115.4 million by 2050[31]. Despite the increasing prevalence of dementia in the older adult population, there is currently no effective treatment. Hence, some studies have investigated targeting modifiable CVRFs to mitigate cognitive decline[31].

The brain depends on a continuous supply of regulated blood flow, therefore, cognitive health and function is partially reliant upon cardiovascular (CV) dynamics[32]. Many studies have focussed on the effect of blood pressure, specifically systolic blood pressure (SBP) and its influence on cognition[33-35]. Cross-sectional research studies have found an association between hypertension (SBP >140 mm Hg; DBP > 90 mm Hg) and cognitive decline in adults aged 55 years or more in various ethnicities[33-35]. Similarly, longitudinal studies observed comparable results, whereby adults aged 60 years and older who were hypertensive or had continually high SBP in midlife, had a higher risk of AD occurrence in late life or suffered from significant cognitive decline[36,37]. See **Table 1** for blood pressure (BP) studies on cognition.

Furthermore, other CVRFs including inflammatory marker variability, decreased total serum cholesterol, lowered high density lipoprotein (HDL), reduced heart rate variability (HRV) and increased arterial stiffness were all associated with cognitive decline[38-40]. See **Table 2** for other CVRFs studies on cognition

Table 1: BP Studies on Cognition

Author	Study Population	CVRF	Main Results
Cross sectional BP Studies			
Kuo et al.[33]	aged ≥65 years old, healthy	SBP	SBP >145 mm Hg linked to impaired executive function
Steward et al.[34]	British African, 55-75 years old	BP	Clinically diagnosed hypertension and cognitive impairment are linked
Andre-Petersson et al.[35]	Swedish Men, aged 68+ years old	BP	BP ≥180/110 mm Hg was related to poorer performance on the neuropsychological test battery
Longitudinal BP studies			
Wu et al.[36]	Chinese, ≥65 years old	21 year follow-up BP	Hypertension (160/95 mm Hg) in midlife was related to a higher risk of AD prevalence in late-life[11]
Waldstein et al.[37]	Baltimore, 60-96 years old	11 year follow-up SBP	SBP (continuous variable) was associated with decreased cognitive performance, and greater cognitive decline when asked to complete a series of neuropsychological tests[12].

Abbreviations: BP, blood pressure; SBP, systolic blood pressure; AD, Alzheimer's Disease; mm Hg, millimeters of mercury

Table 2: Other CVRFs Studies on Cognition

Other CVRFs studies			
Author	**Study Population**	**CVRF**	**Main Result(s)**
Metti et al.[38]	Non-demented, 70-79 years old	Inflammatory marker: C-reactive protein (CRP) over 10 years	CRP variability reflected poor control of, or more, pronounced changes in vascular or metabolic disease over time leading to an associative cognitive decline
Kim et al.[39] and Atzmon et al.[40]	Non-demented, elderly	Total serum cholesterol, high density lipoprotein (HDL)	Lower total serum cholesterol and lower high density lipoprotein (HDL) were connected with reduced cognitive ability
Al Hazzouri and Yaffe[41]	Mexican-American, community-dwelling older adults	Heart rate variability (HRV)	Found an association between reduced HRV and poorer cognitive function
Al Hazzouri and Yaffe[42]	Older adults	Arterial stiffness	Increase in arterial stiffness was coupled with lower cognitive performance. This was observed on measures of global cognition and over several domains of cognition

Other study interventions have improved CVRFs, which subsequently slowed cognitive decline. Burns et al. conducted a study of brain atrophy and cardiorespiratory fitness, specifically VO2peaks (the highest value of volume of oxygen attained during a particular fitness test) in subjects without dementia and subjects with early onset of AD.

They found an increase in VO2peaks were associated with a decrease in brain atrophy in non-demented elderly subjects[43].

The Rotterdam study also observed a higher cerebral blood flow (CBF) velocity and its association with a lower likelihood of getting dementia[44]. Lastly, Fukuhara and colleagues suggested that arterial stiffness could predict cognitive function in the elderly, specifically pulse wave velocity (PWV), which was independently associated with Mini-Mental State Examination (MMSE) scores[45]. Increasing evidence suggests the contribution of CVRFs to cognitive health and therefore, it is imperative to find ways to mediate such risk factors due to their significant role in cognition[32].

Studies that utilized exercise interventions have found beneficial effects on CV health[46]. Exercise is described as a method of physical activity that is a structured routine extended over a period of time with intentions of enhancing fitness, function or health[47]. Exercise training can be administered in various forms such as dynamic/isometric resistance or strength training which improve muscle mass; aerobic exercise (AE) training whereby it decreases arterial stiffness; flexibility and balance training which aid in posture; and mobility training which decreases the risk of falls[46]. Many studies have used exercise, specifically AE to improve CV health in older adults. One study found AE preserved endothelial function with aging and directly induced arterial protection. Seals and Adolph concluded that AE should be used as a “first line” strategy for prevention and treatment of arterial health[48]. Furthermore, a study by Ten Brinke et al., observed after six months of AE training, a significant enhancement in hippocampal volume in older women with possible mild cognitive impairment (MCI)[49]. Although studies have looked at exercise to improve CV health, it is still uncertain whether exercise in its entirety, is the most beneficial method for improving CV health.

Cognitive training (CT) has been considered another form of exercise, specific for the brain, which acts as a protective factor as we age and may be a possible prevention measure for cognitive impairment[50]. For the objective of this systematic review, CT are defined as “structured, repetitive practices on tasks with a distinctive problem, using standardized tasks targeting specific cognitive domains and/or teaching strategies and skills in order to optimize cognition and functioning”[51,52]. Cognitive training interventions incorporate training of executive function networks of the brain to segregate attention and co-ordinate actions more efficiently and effectively[53]. Research suggests that executive control processes and their underlying brain regions are plastic and can be modified by CT[54]. Examples of CT include non-computer based training programs such as a study done by Oshugi et al., who compared a single task (either doing calculations or performing step climbing) and dual task (performing both single tasks simultaneously)[55]. Another study used a novel square stepping exercise, whereby participants had to remember a demonstration of a stepping pattern and then perform it on a mat partitioned by squares[56]. Computer based CT are also used, such as variable priority training developed by Kramer et al.[57], and examined by MacKay-Brandt[58]. This task involves performing two concurrent tasks on a computer. For example, one version of this task required “cutting” a flower image at random locations on the monitor (cutting requires the participant to use the mouse to position an image of scissors over the flower and clicking). Instantaneously, single digits bounded in a box were shown serially in the middle of the monitor whereby participants had to press a number key to indicate the correct sum. Other CT have involved music or a musical instrument[59], choreographed dance[60] or various dual-tasks such as walking on a treadmill while completing another task[23].

Furthermore, studies have also compared CT and AE to examine which method was more beneficial. Klusman and colleagues recognized objective measures of memory and executive function (EF) (Trail Making Test B divided by A) were preserved or enhanced in older women with mild cognitive impairment (MCI; MMSE $\geq$ 20) after receiving 6 months of either CT or AE. Interestingly, cognitive function improved to a similar extent in both individuals receiving CT or AE[61]. This suggests CT may be a possible intervention to reduce the risk of cognitive decline analogous to AE in older adults with MCI, and that CT may pass on similar effects to individuals who are free of MCI.

It is uncertain whether cognitive training will instil similar effects on CV health despite the interrelation between cognitive function and CV health. The exploration of CT with or without an exercise program on vascular health is still critical for the advancement of understanding by which CT, as a type of exercise, can affect CV health in aging. This systematic review aims to: 1) examine the effects of CT, with and without exercise, on SBP in community-dwelling older adults with and without cognitive impairment but no dementia, and 2) identify whether any other CVRFs are improved by CT.

The research question for this systematic review was developed using the PICO: Population, Intervention, Comparison and Outcome(s) (http://learntech.physiol.ox.ac.uk/cochrane_tutorial/), framework. Xiaoili and colleagues investigated the validity and suitability of the PICO framework and confirmed its appropriateness for structuring clinical questions[62]. Our review question is stated as:

Among community-dwelling adults (aged 55 years and older) with and without cognitive impairment, do those who receive CT alone or in combination with any form of exercise have improved vascular health [such as lower blood pressure (systolic and diastolic), higher maximum oxygen uptake (Vo2max), or improved lipids, inflammatory markers (i.e., BDNP, IGF-1)], vascular mechanics (i.e., arterial stiffness, intima-media thickness (IMT), dispensability), and heart rate variability, compared to those who received an alternative therapy.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and statement were used as a protocol for this review[63]. Registration of this systematic review was completed through Prospero, an international prospective register for systematic reviews (registration #CRD42014013876).

Eligibility

Types of Studies

Eligibility for inclusion consisted of trials, irrespective of randomization, which evaluated CT against an appropriate comparator intervention that did not include a CT intervention. Studies used either a randomized controlled trial (RCT) or nonrandomized intervention trial. The article had to address any confounding factors (i.e. race/ethnicity/culture, gender, education, age, CVRFs) and compare study participants to at least one of the possible confounding factors.

Types of Participants

Community-dwelling adult population, aged 55 years or older were considered.

Participants were excluded if they (1) self-reported (based on diagnosis by a physician) or suspected to have dementia based on study specific assessments [(i.e. neurological examination such as the Mini-mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) or other assessment tools], (2) presented with other neurological or psychiatric conditions, including, Parkinson's Disease; Bipolar disease, Schizophrenia, ADHD, Bipolar disorder, cerebral palsy, Horton disease, Downs Syndrome, Epilepsy, Fibromyalgia, Huntington's disease, Intracranial Hypertension, Neurofibromatosis, Tay-Sachs disease, Tourette Syndrome, Traumatic brain injury, or (3) who have not experienced a major cardiovascular event in last 2 years, were included.

Types of Intervention

The intervention of interest was CT. Both computer- and non-computer-based CT interventions were considered. The CT intervention could occur in isolation or in combination with exercise. The following exercise components were accepted: (1) Aerobic exercises (water-based exercises, yard work, dancing, biking, climbing stairs, field sports, basketball, tennis, hockey, football, aerobics); (2) Strength exercises (weight lifting, resistance training, muscle training); (3) Balance exercises (martial arts, tai-chi, qigong); (4) Flexibility exercises (yoga, upper and lower body stretches); and (5) Other type of exercise deemed appropriate by the study authors (i.e. Wii-based exercise program[60], coordination training[64], functional tasks exercises[65]). Cognitive training interventions that also included diet or pharmacological components were excluded. The comparator group had to be an alternative therapy that excluded CT, such as standard or usual care, active control (non-CT group), or allocated to a wait-list group.

Outcome

Main Outcome

The primary outcome of interest was ambulatory SBP (measured in mm Hg). Ambulatory blood pressure gives a valuable sense of how one's blood pressure fluctuates in regular activities performed throughout the day. Blood Pressure patterns over 24 hours could also have inferences about cognitive function, however not many studies have focussed on ambulatory BP[58]. The US Preventative Services Task Force is also considering having an ambulatory blood pressure monitor (ABPM) as an inclusion factor for the screening and diagnosis of hypertension[66]. Therefore, if ABPM's become widely accepted, comprehending its interaction in addition to age-related outcomes such as cognitive function will be beneficial for the population at large[67].

Secondary Outcomes

Other CV outcomes that were considered included: (1) ambulatory DBP, (2) carotid arterial stiffness, (3) other arterial stiffness (not carotid), (4) carotid intima-media thickness, (5) intima-media thickness (not carotid), (6) distensibility, (7) VO2max, (8) heart rate variability, (9) lipids (i.e. triglycerides, steroids, phospholipids), (10) inflammatory markers [(i.e. BDNP, endothelial markers, adhesion molecules, IGF-1, cytokines (i.e. IL-1, IL-6, TNF-α), acute-phase reactants (i.e. fibrinogen, SAA, CRP), white blood cell count)], and (11) other CV outcomes (i.e. cerebral blood flow, pulse pressure, pulse wave velocity).

Sociodemographic Factors

The following sociodemographic factors were considered for influences associated with

CV health. Place of residence was categorized by geographical location, and classified by urban or rural. Race was defined by the following categories: Caucasian, African American, Asian, or other. Sex was categorized by male or female. Level of education was defined as: primary education, secondary education, post-secondary (non-trade), post-secondary (trades), graduate or other. Age was documented by mean, mean interquartile range and/or by categories: 55-64, 65-74, 75-84 and 85+ years.

Information Sources

Studies were identified by searching electronic databases, reviewing reference lists of eligible articles and consulting with experts in the field. The search strategy was developed with the help of experts in the field and aid of an experienced librarian from the Taylor Library, Western University. Restrictions were implemented for English language only and published in 2000 onwards. A limit on date was set due to the rarity of research in CT prior to 2000. The following databases were searched: Pubmed, CINAHL, EMBASE, Scopus, PsycINFO. We also searched secondary sources, including, the Cochrane library, Prospero database, and Google Scholar. Furthermore, we manually searched the reference lists of all included articles and contacted one author to acquire a full text version of their study. The final search was completed in July 2014 with an updated search performed at the beginning of January 2015.

Search Strategy

The following terms were used in the search strategy (note: each term was searched separately and then combined with ‘OR’):

[(brain training” OR “memory training” OR dual tasking OR dual-task OR “mental activity” OR “mental training” OR brain exercise OR brain exercises OR “cognitive training” OR "computer based cognitive training" OR “computerized brain training” OR psychoeducation OR square stepping exercise OR neuropsychological performance)

AND

(vascular OR blood pressure OR artery OR arteries OR cerebrovascular OR neurovascular OR cardiovascular OR “blood flow” OR “arterial compliance” OR blood vessel OR blood vessels OR “carotid artery” OR VO2max OR “arterial stiffness” OR blood flow velocity OR “heart rate” OR “pulse pressure” OR “aerobic fitness” OR “vascular mechanics” OR “peripheral circulation” OR vascular stiffness)

AND

[(“older adult” OR “older adults” OR seniors OR 55+ OR mild cognitive complaint OR cognitive complaint OR mild cognitive complaints OR cognitive complaints, OR senior OR aged OR geriatrics)]

Study Selection

One researcher independently reviewed the title, abstract or description of all trials identified by the literature search. For level 1 screening, the eligibility criteria were kept broad, as outcomes are often poorly reported in titles and abstracts. Studies that aimed to conduct CT in individuals over the age of 55 years were selected. The eligibility criteria were stricter for full-text review and the type of CT intervention, outcomes reported, and study designs were scrutinized to determine if they met the inclusion criteria.

Data Extraction

Two independent researchers extracted data from included studies using standardized extraction forms. Discrepancies were resolved by discussion until a consensus was reached. Data items collected included: study characteristics (i.e. type of intervention, location, length of study, recruitment), subject characteristics (i.e. age, gender, race, education, eligibility, inclusion and exclusion criteria), primary and secondary outcome results (if CV variables were present), details of the CT intervention and comparator group(s), statistical analysis (i.e. statistics used, power calculation), withdrawal and lost to follow-up reasons. The presence or absence of the following comorbidities were also documented: hypertension, dyslipidemia, diabetes, coronary artery disease, cerebrovascular diseases, transient cerebral ischemic attack, coronary heart disease, severe orthopedic limitations, and depression.

Quality Assessment

In order to determine the validity of eligible RCTs, two researchers independently assessed the risk of bias in all of the included studies. The PEDro scale was used to assess study quality and validity of the articles (pedro.org.au). The PEDro scale is an accepted and reliable tool, determined to have sufficient reliability for its use in systematic reviews of physical therapy RCTs[61]. The PEDro scale consists of an 11-item scale with the final PEDro score is based on a maximum score of 10; Item 1, which relates to external validity, is excluded from the final score. See **Appendix A (Table 1)** for details of each item and scoring.

Data Synthesis and Analysis

Data synthesis was conducted from a description of studies and qualitative synthesis of findings; therefore, heterogeneity via a statistical approach was not conducted. Altogether, studies used various forms of CT, length of intervention and outcomes; of which only 2 had the same CV outcome; determined a priori that three studies would need to assess the same outcome in order to conduct a meta-analysis.

RESULTS

Study Selection

The initial literature search identified 640 titles and abstracts, of which 73 were removed for duplicate citations. Of the remaining 567, 556 (98.1%) were excluded because the article: (1) did not explore CT in the context of vascular outcomes (97.4%); (2) did not include any form of CT (88.1%); (3) did not compare CT to any alternative therapy (87.1%); (4) did not screen out patients for dementia (75.2%); (5) did not include an appropriate intervention and comparator (55.4%); (6) did not compare participants to at least one confounding factor outlined (43.9%); and (7) included patients under the age of 55 years (26.3%). Of the remaining 11 articles, 7 (1.4%) of them were excluded because the article: (1) was a protocol study (.35%); (2) was still on-going (.35%); and (3) did not aim to explore CT in the context of managing vascular health (.70%). In total, four studies were included in the systematic review, see **Figure 1** for the CONSORT diagram.

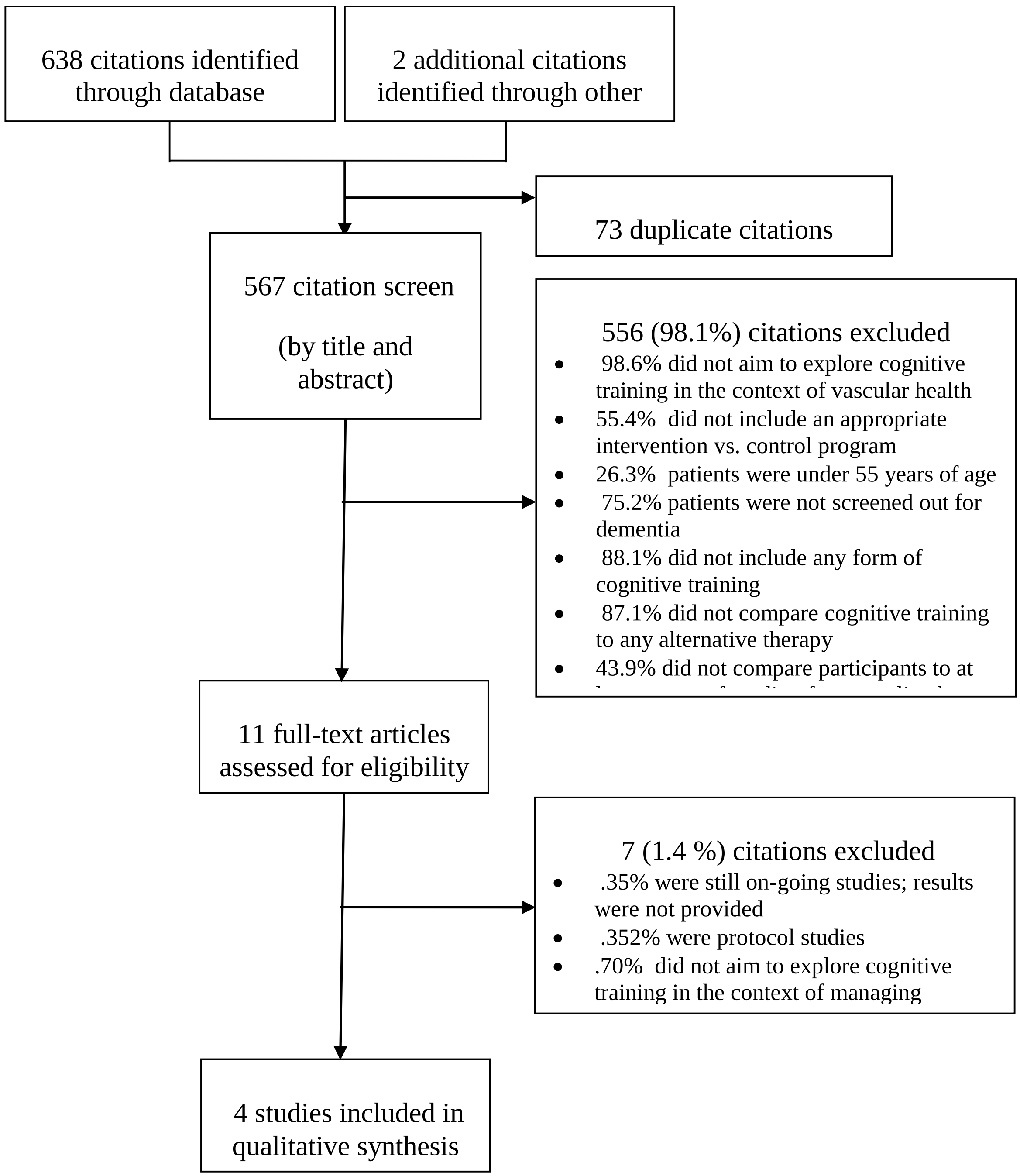


Figure 1: CONSORT Diagram for Systematic Review

Study Design and Study Quality

Study characteristics of the four included studies are presented in **Table 3**. All four studies were published in English, with all but one study having an 8 week intervention period. They all had a parallel group RCT design, and assessed for dementia using a diagnostic tool or by subjective report. They all scored a 6, 8 or 9 out of a perfect score of 10 on the PEDro scale of quality assessment, a valid measure of the methodological quality in clinical trials[70].

All four studies received a point on the PEDro scale for: (1) specifying their eligibility criteria; (2) having similar groups at baseline regarding the most important predictive markers; (3) measuring at least one key outcome of which was obtained from more than 85% of the subjects initial allocation to groups; (4) all subjects received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat," and (5) reporting the results of between-group statistical comparisons for at least one key outcome. All but one study provided both point estimates (i.e. means) and variability measures (i.e. standard deviations) for at least one key outcome.

Table 3: Study Characteristic Details of Accepted Articles

Author, Year	Study Design	Dementia Diagnostic Tool	Type of CT	Training Length	Comparator Group	Covariates
Mozolic et al., 2010[68]	[a]RCT	MMSE score within 2.5 SD of the mean for their age and educational level	Non-computerized Training, targeting attention and distractibility projected on a movie screen	8 weeks	Went to lab and listened to lectures/educational program	-----
Shimzu et al., 2013[59]	[b]RCT	Excluded serious medical conditions that may interfere with participation in study (subjective report)	Movement music therapy (MMT) with Naruko Clapper	8 weeks	Exercise with counting and no music	Age, weight
Fabre et al., 2002[22]	[a]RCT	BEC score of 94.0 (.97)	Israel's Method 8 Themes: • perceptive activities • attention • intellectual structuration • association and imagination • language • spatial marks • temporal marks • associated recruiting	2 months	Leisure activities i.e. painting and choral singing	Age, body mass, height
Linde et al., 2014[69]	[b]RCT	Subjective report	Editing worksheets, selected from CT manual developed & evaluated by Oswald et al.	16 weeks	Inactive waiting control; Standard or usual care	CVD regimen

Abbreviations: MMSE, Mini-Mental State Examination; CVD, Cardiovascular Disease; RCT, Randomized controlled trial. [a]RCT: Parallel; [b]RCT: Factorial

However, none of the studies received a point for blinding their therapists who administered the therapy. Merely two studies received a point for blinding their subjects (to group allocation only). Firstly, Linde and colleagues[69] had the only study to receive a point for having concealment of allocation, thereby avoiding systematic biases. Secondly, Linde and colleagues blinded their assessors who measured at least one key outcome; therefore giving their study the highest score on the PEDro scale of 9 out of 10, see **Table 4**.

Table 4: PEDro Scale

Item Scale	Mozolic et al., 2010[68]	Shimzu et al., 2013[59]	Fabre et al., 2002[22]	Linde et al., 2014[69]
Randomized	Yes	Yes	Yes	Yes
Concealed Allocation	No	No	No	Yes
Baseline Similarity	Yes	Yes	Yes	Yes
Subjects Blinded	Yes	Yes	No	No
Therapists Blinded	No	No	No	No
Assessors Blinded	No	Yes	No	Yes
Outcome from >85% of Subjects	Yes	Yes	Yes	Yes
Intention-to-treat	Yes	Yes	Yes	Yes
Between-group Statistic	Yes	Yes	Yes	Yes
Point & Variable Measures	No	Yes	Yes	Yes
Total Score	**6**	**8**	**6**	**9**

1 point given for yes, 0 points for no

Participants

The included studies contained 226 participants. The mean age of participants in the control group across all studies ranged between 65-77 years old. Similarly, the intervention groups had the same mean age range across all studies. Participant withdrawals from studies included: (1) scheduling restraints or MRI incompatibility; (2) small amount of male enrollment; (3) health complaints; or (4) in some cases, were not reported. All studies included community-dwelling older adults age 55 years or older who were deemed healthy or cognitively impaired, no dementia through a diagnostic assessment or subjective report. See **Table 5** for subject characteristics details.

Cognitive Training

All four studies differed on their intervention. Mozolic and colleagues conducted an 8 week intervention using a non-computerized training program that targeted attention and distractibility[68]. Participants had to supress irrelevant distractors (i.e. short video clips for visual distraction or sound clips for auditory distraction) of people, places, and events while completing tasks requiring detection, classification and/or sequencing visual or auditory presentations of letters, words, and numbers (2-5 mins/task). An active control group was required to attend lab and listen to educational programs[68].

On the contrary, Shimzu et al., also conducted an 8 week intervention but used movement music therapy (MMT) with a Naruko Clapper[59]. The Naruko is a musical instrument made of an uncomplicated clapper mechanism. Participants were instructed to clasp the Naruko and shake it, generating a clapping sound while coordinating with background music.

Table 5: Subject Characteristic Details

Author, Year	Study Site	Total Eligible	Total Female (%)	Withdrawal Reasoning	Total Analyze (C)	Total Analyze (I)	Mean ± SD Age (C)	Mean ± SD Age (I)
Mozolic et al., 2010[68]	cCS	66	55.3	Scheduling constraints or MRI conflict	25	23	69.4±2.4	69.3±3.2
Shimzu et al., 2013[59]	dCS	124	100	Males excluded due to small amount of males	33	58	76.3±5.0	76.5±4.6
Fabre et al., 2002[22]	eCS	32	-----	-----	8	24	65.7±1.5	65.9±1.4
Linde et al., 2014[69]	fCS	70	58.6	Logistic issues, health complaints, participation in other programs, dislikes intervention	13	42	66.7±3.2	67.2±3.3

C: Control; I: Intervention. cCS: USA; dCS: Japan eCS: France; fCS: Germany

The clapper utilizes whole body movement, and is a beneficial exercise for flexibility of joints and strengthening of limbs. The intervention included 5 steps: (1) verbal greetings, (2) warm-up, (3) light exercises, (4) main exercise and (5) relaxation. The control group performed the same exercises as the intervention group however; subjects did not have music or operate the Naruko[59].

For 8 weeks, the Israel method which targets 8 themes of cognitive function was employed by Fabre and colleagues[22]. The session commenced with 15 minutes of explaining memory mechanisms followed by participants working according to the theme of the session. The 8 themes included: (1) perspective activities (sight and hearing) such as remembering details from pictures of people or objects and detecting a particular sound in an auditory text, (2) Attentional activities required reading different texts and summarizing the main idea, (3) intellectual structuration was stimulated by completing word beginnings, (4) association and imagination activities such as finding hidden objects in a picture or finding similar or differential areas in a picture of humans, animals or objects, (5) language activities had to retrieve opposite or complementary words, (6) spatial marked activities were stimulated by drawing the mirror image of different objects, (7) temporal marked activities required ordering in chronological order the news events or personal recollections, and lastly (8) associated recruitment was stimulated by using personal dates (birthdays, anniversaries) to remember banking and social security numbers. On the contrary, the active control group was required to perform leisure activities[22].

Lastly, the longest intervention of 16 weeks was executed by Linde and colleagues[69]. Selected exercises from a CT manual developed by Oswald et al.[24,71], were used. The primary focus of the CT intervention required subjects to edit worksheets either alone, with a partner or in a group. After a 5-minute short-term memory warm-up training, 25-minutes were allocated to practicing: short-term memory, visuospatial skills, information processing speed, concentration, and logical reasoning. At the end of each session, two additional exercises were given as homework. This was the only study that had an inactive, standard care control group[69].

Risk of Bias Across Studies

In order to exclude participants with dementia, various screening tools were used across the four studies. Mozolic and colleagues used the Mini-mental state examination (MMSE)[68], a valid and reliable 30-point questionnaire which is commonly used in clinical and research settings to measure cognitive impairment[72]. Two studies excluded for dementia/serious medical conditions by subjective indication from the participants[59,69]. The BEC 96 questionnaire was performed by Fabre and colleagues[22]. A semantic and fluency task administered to participants to measure cognitive function and detect cognitive issues[66]. All but one study had an active control group in their study[68,59,22]. Generally the mean age of participants differed across all four studies. Two of the studies had a mean age of mid 60's[22,69], whereas the remaining two studies had a much older mean age of late 70's[68,59].

Outcome Measures and Intervention Effects

Cerebral Blood Flow (CBF)

Whole brain CBF was assessed in only one study[68]. However, due to insignificant findings in whole brain CBF, regional blood flow was examined and a significant finding in the right inferior frontal cortex (RIFC) and the mean group difference from pre-post was found. Right inferior frontal cortex was observed following CT that involved a non-computerized training program targeting attention and distractibility projected on a movie screen. A significant increase ($p<.05$) of 15.6 ml/100·g/min (43.6 to 59.2 ml/100·g/min) for the intervention group in RIFC was found. However, the control group, who listened to educational programs in the lab, had a negative difference of 3.9 ml/100·g/min (58.1 to

54.2 ml/100·g/min). Therefore, CT indicated a beneficial effect of the intervention compared to the control group.

Clinical Systolic and Diastolic Blood Pressure (cSBP and cDBP)

Clinical SBP and DBP were assessed by Shimzu and colleagues[59] after completing 8 weeks of training with (intervention group) or without (control group) the Naruko clapper and music. The mean group difference from pre-post is presented. They found a significant decrease in SBP of 8.48 mm Hg (134.86±19.40 to 126.38±15.64 mm Hg; $p=.004$) in the intervention group and no change in the control group with a difference between groups pre-post of $p=.109$. DBP had no change in intervention, control or difference between groups.

Maximum Volume of Oxygen Consumption (VO2max)

Two studies examined changes in VO2max[22,69]. The first study was done by Fabre and colleagues who had their participants complete the Israel method of eight themes[22]. Three different intervention groups were observed: (1) AE training, (2) CT, and (3) combined AE and CT and were compared to a control group that completed leisure activities (i.e. painting, singing etc.). A significant increase in VO2max was found in two of the three intervention groups. The AE training only group had increased the most out of all the intervention and control groups , with a difference of 280 $ml \cdot min^{-1}$ (1350±510 to 1630±146 $ml \cdot min^{-1}$; $p<.05$). The combined intervention group had an increase of 115 $ml \cdot min^{-1}$ (1510±109 to 1625 $ml \cdot min^{-1}$±217 $ml \cdot min^{-1}$; $p<.05$). However, the mental training only group decreased by 69 $ml \cdot min^{1}$ (1060±116 to 999±118 $ml \cdot min^{-1}$; $p>.05$). On the contrary, the control group had a very slight increase in VO2max of 11 $ml \cdot min^{-1}$ (1256±100 to 1265±115 $ml \cdot min^{-1}$; $p>.05$).

The second study was by Linde and colleagues[69]. They observed VO2max before and after 4 months of editing worksheets, selected from a CT manual developed and evaluated by Oswald et al[24,71]. Similar to the study by Fabre and colleagues, 3 different intervention groups were used: (1) physical training, (2) CT, and (3) combined physical training and CT and were compared to an inactive waiting/standard or usual care control group. A significant increase in the physical training only group of 2.69 $ml \cdot min^{-1} \cdot kg^{-1}$ (25.19±8.44 to 27.88±6.25 $ml \cdot min^{-1} \cdot kg^{-1}$; $p<.05$) was observed. In the CT only group, there was a clinically significant increase of 2.53 $ml \cdot min^{-1} \cdot kg^{-1}$ (25.41±7.73 to 27.94±8.30 $ml \cdot min^{-1} \cdot kg^{-1}$; $p<.10$).

Contrary to the findings of Fabre and colleagues, the combined intervention group was the most successful with an increase of 4.52 $ml \cdot min^{-1} \cdot kg^{-1}$ (24.1±9.97 to 28.86±8.72 $ml \cdot min^{-1} \cdot kg^{-1}$; $p<.01$). Furthermore, in the control group, the two studies also differed. The control group significantly increased the most by 5.13 $ml \cdot min^{-1} \cdot kg^{-1}$ (23.90±8.34 to 29.03±7.53 $ml \cdot min^{-1} \cdot kg^{-1}$; $p<.001$) compared to any of the intervention groups[69]. See **Tables 6 and 7** for control and intervention group results.

Table 6: Control Group Results

Author, Year	Control Group	CV Outcome	Baseline				Follow-Up			P-Value
			N	Mean	SD	Time	N	Mean	SD	
Mozolic et al., 2010[68]		CBF-RIPC (ml/100·g/min)	25	58.1	-----	8 weeks	25	54.2	-----	-------
Shimzu et al., 2013[59]	YE	SBP (mm Hg)	21	134.6	15.3	8 weeks	21	135.1	10.6	$p^a = .89$
	OE	SBP (mm Hg)	8	132.5	17.7	8 weeks	8	128.8	22.0	$p^a = .69$
	YE	DBP (mm Hg)	21	78.5	11.2	8 weeks	21	76.9	8.4	$p^a = .49$
	OE	DBP (mm Hg)	7	70.4	9.3	8 weeks	7	70.1	20.0	$p^a = .96$
Fabre et al., 2002[22]		VO2max ($ml \cdot min^{-1}$)	8	1256	100	8 weeks	8	1265	115	$p > .05$
Linde et al., 2014[69]		VO2max ($ml \cdot min^{-1} \cdot kg^{-1}$)	13	23.9	8.3	16 weeks	13	29.0	7.5	$p^a < .01$*

Control YE: Control younger elder; Control OE: Control older elderly; CBF-RIPC: Cerebral Blood Flow in right inferior prefrontal cortex.
P^a: Paired t test, compared before and after in each group; p=/<*: significant

Table 7: Intervention Group(s) Results

Author, Year	Intervention Group	CV Outcome	Baseline			Follow-Up				P-Value
			N	Mean	SD	Time	N	Mean	SD	
Mozolic et al., 2010[68]	Attention and distractibility	CBF-RIPC (ml/100·g tissue/min)	23	43.6	-----	8 weeks	23	59.2	-----	p <.05*
Shimzu et al., 2013[59]	YE	SBP (mm Hg)	32	140.1	17.7	8 weeks	32	129.0	15.3	p^a = .00*
	OE	SBP	26	128.5	19.8		26	125.2	17.1	p^a = .434
	YE	DBP	32	76.4	8.7		32	73.1	9.2	p^a = .05*
	OE	DBP	26	66.9	12.6		26	65.9	8.9	p^a = .613
Fabre et al., 2002[22]	Aerobic Training	VO2max ($ml\cdot min^{-1}$)	8	1350	510	8 weeks	8	1630	146	p<.05*
	Mental Training	VO2max ($ml\cdot min^{-1}$)	8	1060	116		8	999	118	p>.05
	Aerobic + Mental Training	VO2max ($ml\cdot min^{-1}$)	8	1510	109		8	1625	109	p<.05*
Linde et al., 2014[69]	Physical Training	VO2max ($ml\cdot min^{-1}\cdot kg^{-1}$)	15	25.2	8.4	16 weeks	15	27.9	6.3	p^a = .02*
	Cognitive Training	VO2max ($ml\cdot min^{-1}\cdot kg^{-1}$)	11	25.4	7.7		11	27.9	8.3	p^a = .05*
	Physical + Cognitive Training	VO2max ($ml\cdot min^{-1}\cdot kg^{-1}$)	16	24.1	10.0		16	28.9	8.7	p^a = .01*

Intervention YE: Intervention younger elder; Intervention OE: Intervention older elderly; CBF-RIPC: Cerebral Blood Flow in right inferior prefrontal cortex; P^a*: Paired t test, compared before and after in each group; p=/<*: significant*

DISCUSSION

This systematic review examined the effects of cognitive training on vascular health in community-dwelling older adults who were either healthy or cognitively impaired. Four articles qualified for qualitative analysis, demonstrating the paucity of research in this field. The eligible studies were published within the past 13 years (2002-2015), signifying the effects of CT particularly on vascular health in older adults is still in its nascent stage. However, this review still offers direction for research and health care systems about specific modalities that have been tried and found to be successful.

Mozolic et al.[68], used non-computerized CT to significantly increase CBF, whereas Shimzu et al.[59], used music therapy to significantly decrease both SBP and DBP. Although this review cannot definitively state CT interventions are paramount due to limitations in study design, the studies included in this review and others who did not meet the review criteria but still included CT[73,74] have found significant improvement on vascular health.

Furthermore, CVRFs also implicate cognitive function, especially as we age. An editorial in the American Medical Association concluded that the most readily adjustable risk factors of dementia were vascular risk factors[53]. Fukuhara and colleagues explained a possible correlation between atherosclerosis and cognitive impairment whereby preventing the occurrence of atherosclerosis would in turn prevent cognitive impairment[45]. Several longitudinal studies including a one-year study with a non-demented elderly population with subjective memory complaints was founded to have a decline in their MMSE score due to heightened aortic stiffness[75]. Such findings were replicated in the PARTAGE study[76], the Baltimore Longitudinal Study of Aging[14] and The Health ABC sub-study[38]. Similar outcomes were found among late-life blood pressure and cognition where two studies supported the idea of a "U" shaped association concerning blood pressure and a decline in cognitive function[37,77] . Nine studies also confirmed the detrimental effect of high blood pressure (SBP>150 mm Hg) on cognitive function[33-35,78-83]. Therefore, it is imperative to find a definitive prevention strategy or moderator for CV health which will in turn preserve cognitive function, particularly in the older adult population.

Study Limitations

Mozolic et al., demonstrated a significant impact of CT on CBF in older adults, despite being a small pilot study. The addition of a younger population as a control group could verify whether training-induced changes are specific to older adults or could be used for younger adults as well[68]. The Naruko Clapper and music therapy study lowered clinical blood pressure which could be due to the division of their sample into younger and older elderly groups. Furthermore, they encountered a comparatively high dropout rate due to the length of the intervention and traveling distance to test locations and should be addressed in future studies[59]. Fabre and colleagues found significant improvements in VO2max in two of the three intervention (combined AE and CT; and AE training only) groups. They raised a very important variable, anxiety in older adults, to be a possible determinant for the lack of improvement in the mental training group alone[22]. Elderly subjects in general are more anxious compared to younger individuals, which can be due to a loss of attention span[84]. Increased energy in the elderly is required in order to match the performance of a younger adult; as a result, evidence has shown AE to alleviate anxiety[82]. Therefore, groups involving AE diminish anxiety which could lead to better performance compared to mental training alone and should be considered a variable to control, if possible, in future studies[22]. Lastly, Linde et al., found a significant enhancement in control and all intervention groups for VO2max. However, their methodology could be attributable to their impact in VO2max. For economic reasons, a field test was used to estimate VO2max, while still within a valid and acceptable range, field tests can lead to bias by test practice or effects of motivation[23]. Consequently, the increase in cardiovascular fitness among all groups can be partially accredited to either one or both effects. Future studies should utilize undeviating methods to examine cardiovascular fitness[69].

Limitations of this review should also be noted. A second review for level 1 screening was not completed due to time constraints. Moreover, initial study screening with title and abstract may lead to limitations with identifying potential intervention studies despite including articles for full-text review when uncertain about the title or abstract. In addition, one article remained included even though clarification was needed about their study population[52]. Complete data extraction for level 2 screening was not done by the second reviewer because a meta-analysis was not possible based on the results of this review. Lastly, limitations were set to citations published in English and articles from year 2000 onwards, in order to confine the degree of the search yield to a manageable amount of articles; therefore, some could have been missed.

CONCLUSION

Overall, the present review examined the possible effects of CT on vascular health in community-dwelling older adults who were either healthy or suffered cognitive impairment but no dementia. Two of the four articles eligible for qualitative synthesis demonstrated the affirmative effects of CT on vascular health (i.e. SBP and DBP); however, the other two articles revealed a paradoxical impact on vascular health. It still remains unclear whether CT is as favourable other methods for improving vascular health (i.e. aerobic exercise or physical activity), which in turn may improve cognition. Future studies should elicit the most pragmatic method of CT and add to the evidence base regarding whether CT can improve vascular health in older adults.

Thesis Objective

The purpose of this thesis is to elucidate whether a 6-month multiple modality mind-motor (M4) exercise program elicits similar effects on clinical resting systolic blood pressure (SBP) and diastolic blood pressure (DBP), and 24-hour ambulatory systolic blood pressure (24-Hr SBP) and diastolic blood pressure (24-Hr DBP) in community-dwelling older adults (aged 55 years and older) with subjective memory complaints, compared to a 6-month multiple modality (M2) exercise program administered alone.

Secondary objectives

1) Investigate whether M4 improves 24-hour, daytime, and nighttime peak systolic blood pressure (sbppk); peak diastolic blood pressure (dbppk); heart rate (HR); common carotid arterial stiffness [(intima-media thickness (IMT) and arterial compliance (AC)]; blood flow velocity [systolic pulse wave velocity (Psv), diastolic pulse wave velocity (Pdv), end-diastolic pulse wave velocity (Pedv) and average pulse wave velocity (Pavg)]; and cardiovascular (CV) fitness (maximum volume of oxygen uptake;VO2max), to a similar extent as M2.
2) Determine if age (younger elderly, YE; versus older elderly, OE) has an impact on the improvement of vascular health (24-hour ambulatory and clinical resting blood pressure (BP), arterial stiffness, blood flow velocity and cardiovascular fitness) between M2 and M4.
3) Establish whether a difference exists between sex and vascular health (24-hour ambulatory and clinical resting BP, arterial stiffness, blood flow velocity and cardiovascular fitness) improvement among M2 and M4.

Hypotheses

The M4 and M2 group will have similar improvements in 24-hour ambulatory and clinical resting SBP and DBP.

Secondary Hypotheses

1) 24-hour, daytime and nighttime sbppk, dbppk, HR, carotid IMT and AC, Psv, Pdv, Pedv, Pavg and VO2max will all improve to a similar extent in both M2 and M4 groups
2) The YE adults will have greater improvements in vascular health (blood pressure, carotid IMT, carotid AC, VO2max and blood flow velocity) compared to older adults in both M2 and M4
3) Females will have greater improvements in vascular health (blood pressure, carotid IMT, carotid AC, VO2max and blood flow velocity); compared to males in both M2 and M4 groups

Chapter 3: Methods

Subjects

Participants were recruited through various newspaper ads and flyers in local establishments, including doctor's offices in Woodstock, ON. Individuals considered for this study were 55 years of age or older who had a subjective cognitive complaint including memory or thinking skills and preserved instrumental activities of daily living [based on the Lawton-Brody Instrumental Activities of Daily Living (IADL) scale[85]]. Participants were excluded if they (1) were self-reported or suspected to have dementia (i.e. MMSE score <24); (2) had other significant neurological or psychiatric conditions (i.e. Parkinson's disease, Bipolar disorder, Schizophrenia etc.); (3) severe sensory impairment (i.e. blind); (4) previous history of severe CV conditions in the past 2 years (i.e. myocardial infarction, end stage congestive heart failure, end stage renal disease, stroke etc.); (5) significant orthopedic conditions (i.e. severe arthritis); (6) blood pressure <180/100 mmHg or <100/60 mmHg; (7) major depression [based on CES-DS (score ≥16)] and clinical judgement of primary physician; (8) unable to comprehend questionnaire material; and (9) any other reason that would impact ability to fully take part in intervention (i.e. cannot commit to approximately 80% of exercise sessions).

All participants gave written informed consent. The study was approved by Western University Research Ethics Board for Health Sciences Research Involving Human Subjects (**Appendix D**), Lawson Health Research Institute Research Ethics Board approval by CRIC to utilize hospital resources from Parkwood Hospital (**Appendix E**), Clinical trial protocol was registered at clinicaltrials.gov (**Appendix F**).

Study Design

Screening Assessment

Participants underwent a screening assessment. Concurrent medical conditions given verbally, medical history, medications and three seated blood pressure (BP) measurements were collected (Omron Healthcare, Automatic Blood Pressure Monitor, Model 1A2, Japan). Questions were asked regarding their memory and thinking skills prior to assessing their cognitive function using standardized questionnaires including the Mini Mental State Examination (MMSE)[86], the Montreal Cognitive Assessment (MoCA)[87], and an assessment of their ability to engross in daily activities using the IADL[85]. The determination of whether individuals suffered from depression was examined through the Center for Epidemiologic Studies: Depression Scale (CES-DS)[88]. If found to have severe untreated depression (score over 16/60), their family physician was contacted for further information and consultation with the primary investigator, Dr. Petrella to determine best course of action.

Eligible Participants

Eligible participants completed a 3-day baseline assessment prior to commencing the 6-month exercise classes. Similarly, the 3-day assessment was conducted at the end of the 6-month intervention period. The first two days of assessments took place at Salvation Army Church (Woodstock, ON) and the third day took place at the Aging, Rehabilitation & Geriatric Care (ARGC) Research Centre located in the Parkwood Institute (London, ON). On the first day, participants were asked a few questions regarding their general health and current level of physical activity using the Phone-FITT questionnaire[89]. Subjects were then introduced to Cambridge Brain Sciences (CBS), a computer-based cognitive battery (www.cambridgebrainsciences.com). The information retrieved from the 12 computer games targeted specific domains of cognitive function including memory, concentration, reasoning and planning (see Appendix B, Table 1 for description and scoring rubric). On the second assessment day, participants played the 12 computer games in their entirety and their results were recorded. On the third day, participants underwent a series of measurements including: i) vascular measures: 24-hour ambulatory BP (Spacelabs™ ABPM, Model 90207, Spacelabs Inc., Redmond WA, USA), clinical resting BP with an automated oscillometric monitor (BP was measured (BpTRU™, VSM MedTech Ltd., Coquitlam, BC), and a carotid artery ultrasound (2-D Ultrasound; GE Vingemed System 5); ii) gait and mobility using the reliable and validated GAITRite system (platinum version)[90], which uses a sensory walkway mat connected to a software to record spatio-temporal gait characteristics; and iii) sensorimotor eye-tracking assessment (EyeTrac6: Applied Sciences Laboratories, Bedford MA) measuring anti- and pro-saccade reaction time and errors.

Cardiovascular Assessments

Only the measurements used in this thesis will be described in detail below.

24-Hour ambulatory blood pressure

At the end of day 1 or day 2 assessments, participants were fitted with a 24-hour ambulatory BP monitor. The monitor was worn once at baseline and at the end of the 6-month intervention. Ambulatory BP measures consisted of average 24-hour, daytime and nighttime SBP, DBP, sbppk, dbppk, mean arterial pressure (MAP) and heart rate (HR) recordings. The monitor took a total of 40 readings over the 24-hour period. One measurement was taken every half hour during the day between 06:00-22:00, and one measurement was taken every hour from 22:00-06:00. The monitor gave a five second warning beep as an indicator to the participant to relax their arm prior to inflation of the cuff. The monitor beeped once to indicate completion of a successful measurement or beeped repeatedly to indicate an error. In case of measurement error, the cuff automatically inflated two minutes later in an attempt to obtain a successful measure. Participants were asked to not shower during the 24-hour period in order for the cuff to remain on their arm for the entire 24-hour period.

A BP diary was also given in order for each participant to record any events that could cause their BP to increase (i.e. stressful event, laughing hysterically, exercising, etc.). First participant asked to wear for another 24 hours where possible. Average SBP, DBP, peak SBP and DBP, MAP, and HR for daytime, nighttime and an overall 24-hour summary were recorded along with hourly readings. The cut-off for an adequate amount of readings was 50% (20 successful readings) for statistical analysis, otherwise the participant was asked to wear the monitor for another 24 hours.

Ambulatory BP measures give an accurate sense of how the participant's BP fluctuates throughout the day. More readings are taken throughout the day than at night because that is the time when the participant is more active/mobile. Therefore, taking more frequent measures of BP during the day will give a more accurate depiction of the participant's

BP. Nighttime BP was taken less frequently due to the fact that older adults are more sedentary at night.

Clinical Resting BP

Clinical resting BP is comparable to measures of what a participant would take if done themselves or at a doctor's office. On the third assessment day, participants reported to the laboratory (Aging, Rehabilitation and Geriatric Care Research Centre, Parkwood Hospital, London, Ontario, Canada) after abstaining from vigorous exercise (for 24 hours), alcohol (for 24 hours), caffeine (for 12 hours), smoking (for 12 hours) and fasted for a minimum of four hours prior to their appointment to standardize each participant prior to their ultrasound[91]. A BP cuff was secured around the left upper arm (unless contraindicated by other medical issues) approximately two centimeters proximal to the antecubital fossa. After five minutes of seated rest, with back and arms supported and feet flat on the floor, three brachial artery SBP, DBP and HR were measured in triplicate with two minute intervals between cuff inflation[91.]. The averages of the last two measurements were used in analysis. Participants were instructed to relax and remain still and quiet throughout the duration of BP measurements.

Carotid artery intima-media measurement

Following BP measurements, a common carotid artery ultrasound was performed. The carotid artery is an ideal area as it is superficial, easy to access and covers the aorta that demonstrates the greatest age-related stiffening[92]. In almost all cases with few exceptions, the same investigator was used to perform all carotid artery ultrasounds at baseline and 6-months. A second investigator performed the ultrasound at random in order to examine inter-rater reliability. A checklist was completed with each participant preceding the ultrasound, ensuring the participant followed instructions regarding no exercise, alcohol, caffeine, smoking or food. If deviated, a note was made on the checklist of what they ate or did and what time it occurred in reference to their ultrasound appointment. The participant was left to lay supine on the bed for ten minutes to regulate their blood flow velocity prior to connecting them to an electrocardiogram (ECG) to monitor their beat-to-beat HR. Two electrodes were placed two finger-widths below the clavicle, one 12 cm left of the sternum and the other, 12 cm to the right of the sternum. A third electrode was placed two finger-widths above the participant's right ilium.

The right common carotid artery was imaged in all participants with their heads turned approximately 45º towards the left. A 10 Mhz transducer was placed longitudinally along the right common carotid artery to obtain two-dimensional B-mode ultrasound images (Vingmed System 5, GE Ultrasound A/S, Horton, Norway). Image standardization of the carotid artery was done whereby all measurements were taken 2-4 cm away from the carotid artery bulb. Minimum diameters (diastolic), measuring from wall to wall (vessel diameter) commonly coincided with the QRS peak on the ECG. Maximum diameters (systolic) were measured from the top of the wall to the outer edge/bottom of the endothelial layer, which commonly coincided with the T peak on the ECG, however sometimes this had to be done through visual inspection as minimum and maximum diameters did not occur according to the ECG. Averages of 3 values for systolic and diastolic were used for carotid AC calculations, by which carotid AC was determined by using the following equation:

$$\text{Carotid AC} = \Delta D/\Delta P \qquad \text{(Equation 1)}$$

$$\text{Carotid AC} = [\pi(\frac{Dmax}{2})^2 - \pi(\frac{Dmin}{2})^2]/\Delta P$$

where ΔD is the change in arterial diameter from systole (D_{max}) to diastole (D_{min}), and ΔP is the tonometrically-obtained arterial pulse pressure[93-95].

Carotid IMT was measured on a frozen-frame image, which was magnified to achieve a higher resolution of detail and accuracy. Carotid IMT was measured by the subtraction of the lumen diameter from the arterial diameter, which resulted in the thickness of endothelium in millimeters. Carotid IMT was obtained from three contiguous sites within a 2 cm range, the mean of these values were used in statistical analysis[96]. Normative values for carotid IMT for ages 50-59 years is 0.85, while adults 60 years or more generally have an IMT of 1.05[97].

Carotid artery blood flow velocity measurement

Blood flow velocity looks at the rate at which blood flows through the artery to and from the heart and the brain. Selecting "pulse wave" on the ultrasound machine, allowed a different view on the monitor that required the adjustment of "velocity range" and the angle at which blood is flowing. The shorter the velocity range, the larger the signal. Doppler ultrasound was used to collect the pulse wave for 60-72 seconds. Three consecutive pulse waves were chosen based on similar image properties among them. Output recorded for statistical analysis included peak systolic velocity (Psv), peak diastolic velocity (Pdv), end-diastolic velocity (Pedv) and average velocity (Pavg).

Normative values for blood flow velocity in the common carotid artery for adults aged 60-85 years[98].

Once the ultrasound component was completed, participants continued to lie on the bed as a supine brachial artery BP measurement was done once by placing the same BP cuff and monitor used for clinical resting BP measures. Participants were offered a standardized snack (granola bar and juice box) upon completion of the ultrasound.

CV Fitness (VO2max)

The last CV assessment was a step test, which was completed at baseline, half-way through the intervention at 3-months and at 6-months. The step test required the participant to climb up-and-down two sets of stairs 20 times while timed with a stop-watch. This assessment was used to determine the predicted VO2max for the participant and also provide a target heart rate for when they attended the exercise class. The equation used to calculate VO2max through Microsoft Excel was the following:

$$VO2\max\left(\frac{\frac{ml}{kg}}{min}\right) = VO2\ (220 - age - 73 - \frac{(sex \times 10)}{HR - 73 - (sex \times 10)}$$

$$VO2\max\left(\frac{\frac{ml}{kg}}{min}\right) = \frac{1.8 \times work\ heart\ rate}{body\ weight \times sex}$$

where HR is the heart rate at final stage, 0 represented for men and 1 represented for women[99].

Randomization

At the end of day 3, the randomization sequence was generated by one of the study investigators; and the coordinator was concealed to allocation (used numbered, opaque envelopes) using a randomization function (RANDBETWEEN) in Microsoft Excel. Assessors were blinded to group allocation.

Exercise Intervention

Both exercise groups were led by seniors fitness instructors who were certified through the Canadian Centre for Activity and Aging (CCAA). Each exercise session was 60-minutes in length, conducted 3 times a week for 6 months (see Table 1 for Intervention details).

Multiple Modality (M2) Exercise only group

The multiple modality (M2) exercise is a standard combined fitness class for older adults and was developed and guided by the CCAA classes (www.uwo.ca/actage). The M2 only group was structured to receive: 1) 5 minute warm-up targeting major joints and slowly increasing heart rate, 2) 20 minutes of moderate to vigorous intensity aerobic exercise as defined by ACSM guidelines for older adults[100], 3) 5-minute cool-down to safely decrease heart rate, 4) 10 minutes of resistance training of all major muscle groups including core strengthening exercises, 5) 15 minutes of balance training and, 6) 5 minutes of stretching.

Multiple Modality Mind-Motor (M4) intervention group

The M4 group was similar to the M2 group except modified to incorporate 15 minutes of mind-motor exercise. The mind-motor exercise component is best described as a visuospatial working memory task, with a stepping response. It is a low-cost, indoor exercise program (i.e., Square Stepping Exercise (SSE)) originally designed to improve balance and lower extremity functioning in older adults[101]. The SSE utilizes a floor mat grid. In order to successively advance across the mat (motor task), participants were required to memorize stepping patterns which get progressively more complex (visuospatial working memory task) [see **Appendix B. Table 2**]. Both groups were designed to have the same duration and similar exercises in order to control for socialization and activity in general.

Table 1: Intervention Details

M2: Multi-Modality Exercise (Exercise Control)	M4: Multi-Modality, Mind-Motor (Exercise Intervention)
Warm-up (5 minutes) o Light aerobics o Dynamic range of motion of the major joints	**Warm-up (5 minutes)** o Light aerobics o Dynamic range of motion of the major joints
Aerobic Exercise (20 Minutes) o Large rhythmical endurance activities (e.g., walking, marching, sequenced aerobics) o Keep HR continuously in target zone (i.e. not interval training) o Moderate to vigorous intensity Rating perceived exertion (RPE): 5-8 on scale of 0-10 Participants to check HR ½ way through and at end of aerobic exercise. Participants will record final RPE and HR.	**Aerobic Exercise (20 Minutes)** o Large rhythmical endurance activities (e.g., walking, marching, sequenced aerobics) o Keep HR continuously in target zone (i.e. not interval training) o Moderate to vigorous intensity Rating perceived exertion (RPE): 5-8 on scale of 0-10 Participants to check HR ½ way through and at end of aerobic exercise. Participants will record final RPE and HR.
Aerobic Cool Down (5 minutes) o Safely bringing heart rates down	**Aerobic Cool Down (5 minutes)** o Safely bringing heart rates down
Resistance Training (10 minutes) o Therabands, wall or chair exercises, core strengthening o Day 1 – Upper body focus o Day 2– Lower body focus o Day 3 – Core focus	**Resistance Training (10 minutes)** o Therabands, wall or chair exercises, core strengthening o Day 1 – Upper body focus o Day 2 – Lower body focus o Day 3– Core focus
Balance & Sham Training (15 minutes) o Keep HR **BELOW** target zone o Dynamic, static and functional balance o Breathing and relaxation exercises o Finger exercises o Range of motion (e.g., arm circles)	**Mind-Motor Training (15 minutes)** o Keep HR **BELOW** target zone o Square Stepping Exercise (SSE)
Stretching (5 minutes)	**Stretching (5 minutes)**
TOTAL: 60 minutes **60 min Multi-Modal Exercise Training**	**TOTAL: 60 minutes** **45 min Multi-Modal Exercise Training** **15 min Mind-Motor Training**

Table created by: Gill, DP and Stuckey M, M4 Grant study protocol submission.

Statistical Analysis

This study is built off of a larger study whereby a proposed 130 participants (65 participants per group) was an agreeable sample size. The sample size calculation was based on the primary outcome, cognition, with 80% power at the 5% significant level to detect an effect size of 0.55[102,103]. A subsample of the data was collected for the purpose of this study, to examine secondary outcomes; therefore analyses were exploratory. A sample size calculation using GPower 3.1 free software, was performed after the study was completed, with 80% power at the 5% significant level to detect an effect size of 0.65. The primary outcomes of interest for the current study were difference between groups in the following variables: 24-hour SBP, 24-hour DBP, clinical resting SBP and DBP, after the M2 and M4 exercise intervention.

An independent t-test was utilized to assess any baseline differences between group (M2 and M4), age (YE and OE), and sex (male and female). Continuous variables were checked per approximately normal distribution prior to statistical tests. All mean change score outcomes were visually inspected for normality through histograms and the Shapiro Wilks statistic. Data are conveyed as mean±standard deviation (SD), unless otherwise stated. An ANCOVA was used for all mean change outcomes. Outputs recorded from the analyses were estimate mean change, 95% confidence intervals (95% CI) and p-values. Each outcome was a separate analysis. Group was the fixed factor and baseline was adjusted for the outcome of interest. Two sensitivity analyses were conducted for each outcome: 1) analyses were stratified for age and sex and created a separate stratum, and 2) analyses were restricted to all-completers (i.e., 41 participants). Interpretation is based primarily on point estimates and 95% confidence intervals (CIs). All statistical tests had significance set at $p<.05$. SPSS for Windows (Version IBM SPSS Statistics 20) was used to perform all statistical analyses.

Chapter 4: Results

The results are divided into three sections. The first section focuses on all CV outcomes compared by group (M2 vs. M4). Although the gold standard is to include all participants randomized regardless of compliance (intent-to-treat) which balances known and unknown confounders, at the end of the section, a table with compliant participants (80%+) only are included to view the impact of the actual intervention. The second section focuses on all CV outcomes compared by group and age. The last section focuses on all CV outcomes compared by group and sex.

4.1 Descriptive Measures

Overall, 122 participants inquired about the study however, 33 participants were excluded: 1) 23 participants were deemed eligible however; they declined to participate in the study because of time commitment or personal issues; 2) 10 participants were ineligible due to the study's specific criteria including: i.2 participants did not have a cognitive complaint; ii. 5 participants had a significant neurological or neuropsychological condition (i.e. Bipolar Disease, Dementia, Alzheimer's disease); iii. 1 participant scored less than 24 on the MMSE; iv. 1 participant had extreme hypertension, greater than 180/100; v. 1 participant had severe depression (scored 41/60).

A total of 89 participants were recruited and assessed at baseline (27 males, 61 females) which were included for baseline characteristics, however 4 participants with baseline data dropped out during the intervention. See **Figure 1** for consort diagram.

From the 89 participants recruited, 74 participants completed the study however, only 41 participants adhered to a minimum of 80% attendance (absent for a total of 14 classes or less) for the exercise classes. 33 individuals did not meet the 80% compliance however their data was still used in statistical analyses. Deviations from compliance were due to scheduled vacations, medical surgeries or personal reasons.

Demographics and medical history are located in **Table 1** by group (M2 compared to M4).

The M2 group contained 41 participants, whereas the M4 group had 48 participants. The M2 group's average age of 66 years was younger by one year compared to the M4 group respectively. Majority of the participants were Caucasian with the exception of 2 African Americans and 1 participant classified as 'other' ethnicity. More than half of the participants were married in both groups and had the same years of average education (14 years) received. BMI was nearly the same between the two groups with M2's mean BMI of 30.26 and M4's mean BMI 29.14. It is suggested by MedlinePlus, older adults should have a BMI slightly higher (between 25-27) as oppose to under 25, due to potential protective factors such as osteoporosis (nlm.nih.gov/medlineplus/osteoporosis.html). More than half of participants drank alcoholic beverages on a weekly basis in both groups, with each group having one person who smoked concurrently. Two assessments were used to determine whether any cognitive impairment existed. The first assessment was the Mini-Mental State Examination (MMSE), and the second assessment was the Montreal Cognitive Assessment (MoCA), by which both had a maximum score of 30. The average scores were nearly the same for both groups on the MMSE (mean score of 29), and MoCA (mean score of 25). An MMSE score of <24 indicates an increased odds of dementia, a range of 24-30 has very little severity and translates to no cognitive impairment[86]. A MoCA score of 26 or greater is considered normal for older adults[135], therefore, our study population scored high on the MMSE but had an average score on the MoCA, just below the accepted range, indicating some display of cognitive impairment.

Medical history and medication was documented, specifically any cardiovascular medication or medications that influence the cardiovascular health. A total of 49 participants were diagnosed by a physician as hypertensive, with 31 individuals who were medicated. In total, 34 participants were diagnosed with high cholesterol, but only 22 participants were treated with medication. There were 8 participants with diabetes; however, only 7 of them were medicated. A total of 13 participants reported having heart trouble with all of them treated for with medication including blood thinners, heart or other CV medication.

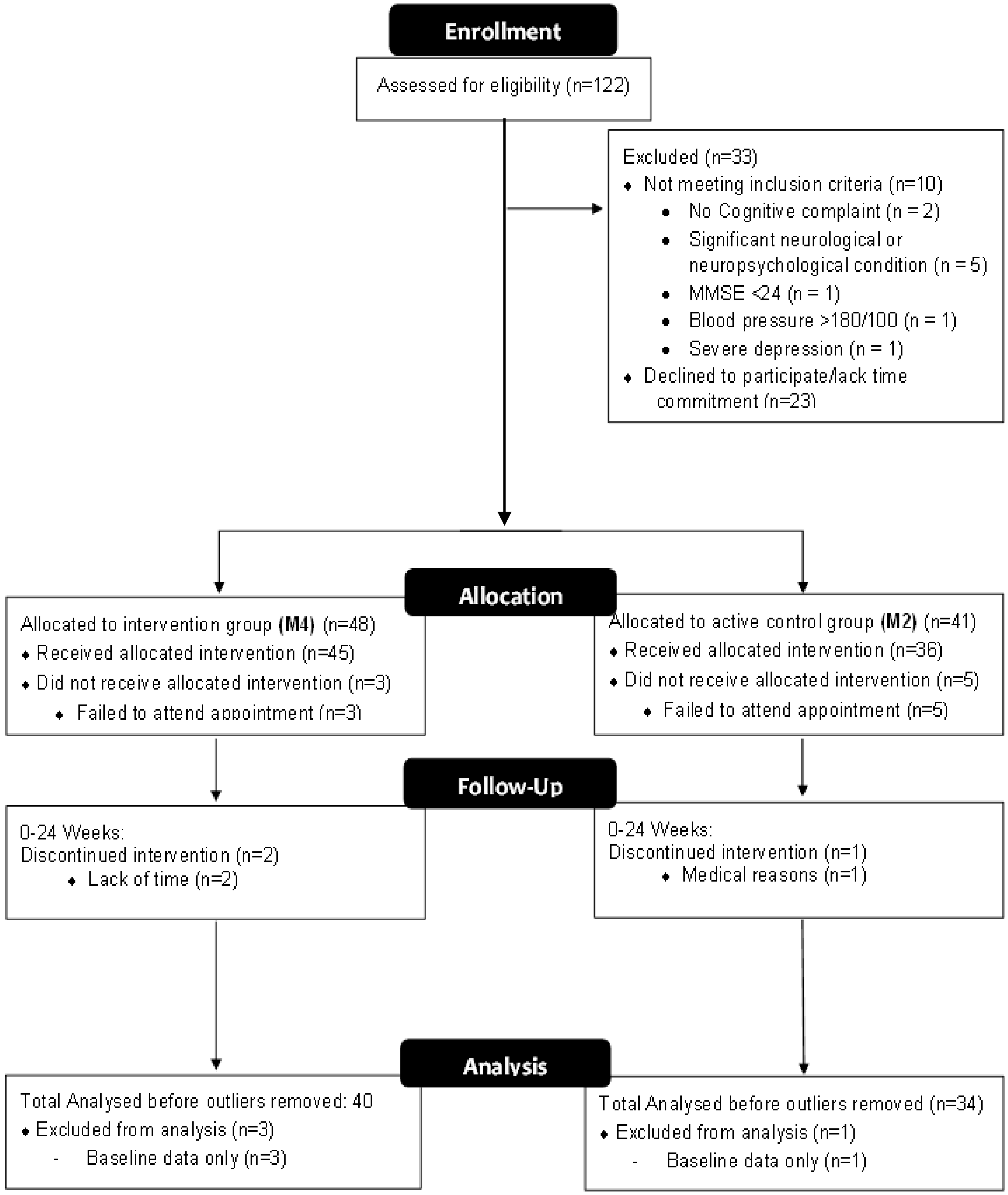


Figure 1: Consort Diagram

Table 1. Demographics and Medical History by Group

Characteristic	M2 (n = 41)	M4 (n = 48)
Age, y, mean (SD)	66.90 (6.38)	67.77 (7.46)
Female Sex, No. (%)	31 (75.61)	31 (64.58)
Caucasian, No. (%)	40 (97.56)	46 (95.83)
Married, N (%)	24 (58.54)	27 (56.25)
Education, y, mean (SD)	13.61 (3.36)	13.17 (2.70)
BMI, mean (SD)	30.26 (6.57)	29.14 (4.09)
Drink alcoholic beverages, No. (%)	25 (60.98)	28 (58.33)
Current Smoker, No. (%)	1 (2.44)	1 (2.10)
Former Smoker, No. (%)	19 (46.34)	25 (52.08)
MMSE score (max 30), mean (SD)	29.05 (1.18)	29.00 (1.20)
MoCA score (max 30), mean (SD)	25.59 (2.56)	25.23 (2.81)
Medical History		
Hypertension, No. (%)		
Total (n = 49)	20 (40.82)	29 (59.18)
Medicated, (n = 31)	12 (38.71)	19 (61.29)
High Cholesterol, No. (%)		
Total (n = 34)	16 (47.06)	18 (52.94)
Medicated (n = 22)	8 (36.37)	14 (63.64)
Diabetes, No. (%)		
Total (n = 8)	3 (37.50)	5 (62.50)
Medicated (n = 7)	3 (42.86)	4 (57.14)
Other CV conditions (i.e. COPD), No. (%)		
Total (n = 13)	7 (53.85)	6 (46.15)
Medicated (n = 13)	3 (23.08)	10 (76.92)

Abbreviations: BMI, body mass index; MMSE, Mini-Mental Status Examination; MoCA, Montreal Cognitive Assessment; pVO2max, Predicted Maximal Oxygen Uptake; [a] Data were missing for pVO2max score in 2 participants and for body mass index in 1. Percentages are calculated excluding missing values (where applicable). [b] Participants were asked to rate their memory on a scale of 5 (from much better to much worse); [c]Other CV conditions Total was for heart trouble only due insufficient data for any other CV conditions recorded, medicated individuals included blood thinners, heart or arterial medication

Baseline CV outcomes by group are presented in **Table 2**. All CV variables at baseline were approximately normally distributed which were confirmed by normality tests. If they were not significant, an appropriate log transformation would have been done to normally distribute the data.

Table 2: Baseline CV Outcomes by Group

Baseline CV Outcomes	M2		M4	
	N	Mean ± SD	N	Mean ± SD
Ambulatory BP				
24-Hr Systolic BP	38	130.00 ± 14.35	47	127.26 ± 11.73
24-Hr Diastolic BP	38	74.37 ± 8.92	47	72.98 ± 8.47
24-Hr peak systolic BP	38	157.58 ± 17.48	47	153.83 ± 17.51
24-Hr peak diastolic BP	38	95.84 ± 11.25	47	92.83 ± 10.78
24-Hr MAP	38	94.32 ± 9.99	47	91.94 ± 10.06
24-Hr HR	38	71.68 ± 6.87	47	71.57 ± 8.61
Day Systolic BP	38	132.13 ± 14.34	47	129.47 ± 11.58
Day Diastolic BP	38	76.11 ± 9.24	47	74.85 ± 8.89
Day peak systolic BP	38	157.08 ± 18.24	47	153.51 ± 16.00
Day peak diastolic BP	38	95.74 ± 11.68	47	92.83 ± 10.78
Day MAP	38	96.26 ± 10.24	47	94.40 ± 9.06
Day HR	38	72.84 ± 7.36	47	72.87 ± 8.77
Night systolic BP	38	121.13± 16.48	47	116.62 ± 20.37
Night diastolic BP	38	66.74 ± 8.99	47	65.53 ± 8.48
Night peak systolic BP	38	138.74 ± 17.01	47	133.72 ± 17.49
Night peak diastolic BP	38	80.66 ± 9.40	47	77.28 ± 10.14
Night MAP	38	86.37 ± 10.54	47	84.96 ± 9.34
Night HR	38	66.68 ± 6.50	47	66.55 ± 9.19
Clinical Resting BP				
SBP	41	142.05 ± 19.24	48	136.25 ± 17.05
DBP	41	83.00 ± 11.01	48	81.29 ± 10.86
Stiffness and Blood Flow				
Carotid IMT	41	.69 ±.16	48	.65 ±.13
Carotid AC	39	.83 ±.35	46	.90 ±.32
Psv	41	59.65 ± 17.07	48	60.72 ± 14.65
Pdv	41	17.11 ± 4.80	48	16.92 ± 4.97
Pedv	41	18.47 ± 5.20	48	19.40 ± 8.48
Pavg	41	29.96 ± 8.25	48	30.48 ± 8.07
CV Fitness				
VO_{2max}	41	25.56 ± 8.38	48	27.44 ± 8.40

Abbreviations: Estimate of Δ**,** estimate of change; BP, blood pressure; Hr, hour; CV, Cardiovascular 24-HR MAP, 24-hour mean arterial pressure; 24-Hr HR, 24-hour heart rate; Day MAP, daytime mean arterial pressure; Day HR, daytime heart rate; Night MAP, nighttime mean arterial pressure; Night HR, nighttime heart rate; Carotid IMT, carotid intima-media thickness; Carotid AC, carotid arterial compliance; Psv, peak systolic velocity; Pdv, peak diastolic velocity; Pedv, end-diastolic velocity; Pavg, average velocity; VO_{2max}, maximal oxygen uptake. [a]Participants included in N, completed baseline and 6-month data with outliers removed. [b]Values are mean ± SD. [c]All ambulatory measures obtained from participants with 50% successful readings. [d]Clinical resting BP used the average of 2nd and 3rd readings.

4.2 Results by Group

Results between groups can be found in **Table 3** and **Figure 2.** Only two CV outcome variables, there was a significant difference between groups (M2 group was used as the reference) from the ANCOVA analysis. Nighttime peak SBP, increased after the 6 month intervention period compared to the M2 group. The mean group difference after 6-months revealed an average decrease change of 6.55 mmHg (95%CI: -12.90,-.10; p=.04) between the two groups. Clinical resting SBP also improved significantly more compared to the M2 group. Between group difference revealed an average decrease of 6.99 mmHg (95%CI: .60, 12.37; p=.03).

Although not statistically significant (p<.05), two blood flow velocity variables showed clinical significance. Pdv showed trends towards worsening in the M4 group after the intervention whereas Pedv showed improvement in the M4 group. Pdv between the two groups, had an average decrease of 1.22 mmHg (95%CI: -2.59, .15; p=.09). The between group differences for Pedv revealed a decrease by 1.22 mmHg (95%CI: -2.59, .15; p=.08).

Table 3: CV Outcomes Mean Change between M2 and M4 after 6 Months

CV Outcome Variables	Between Group Differences			
	Estimate Mean Δ	**95% C.I (lower bound, upper bound)**		**P-value**
Ambulatory BP				
24-Hr Systolic BP	-.46	-4.03	3.10	.80
24-Hr Diastolic BP	.14	-2.16	2.43	.91
24-Hr peak systolic BP	-1.38	-6.30	3.54	.58
24-Hr peak diastolic BP	-1.74	-6.08	2.61	.43
24-Hr MAP	-.77	-2.96	1.43	.49
24-Hr HR	-1.01	-3.81	1.80	.48
Day Systolic BP	-.38	-3.73	2.96	.82
Day Diastolic BP	-1.17	-6.76	4.42	.68
Day peak systolic BP	-.08	-4.69	4.53	.97
Day peak diastolic BP	-.82	-.490	3.26	.69
Day MAP	-.69	-3.37	1.99	.61
Day HR	-1.08	-3.89	1.73	.45
Night systolic BP	-1.92	-6.53	2.69	.41
Night diastolic BP	.29	-2.69	3.26	.85
Night peak systolic BP	-6.55	-12.90	-.19	.04**
Night peak diastolic BP	-.12	-4.92	4.69	.96
Night MAP	1.11	-1.99	4.21	.48
Night HR	-1.42	-4.24	1.41	.32
Clinical Resting BP				
SBP	6.99	.60	13.37	.03**
DBP	2.82	-.86	6.51	.13
Stiffness and Blood Flow Velocity				
Carotid IMT	-.03	-.08	.02	.17
Carotid AC	.06	-.04	.16	.23
Psv	-3.24	-8.03	1.55	.18
Pdv	-1.26	-2.71	.19	.09*
Pedv	-1.22	-2.59	.15	.08*
Pavg	-1.90	-4.26	.47	.11
CV Fitness				
VO2max	.28	-1.70	2.26	.78

Abbreviations: Estimate of Δ, estimate of change; BP, blood pressure; Hr, hour; CV, Cardiovascular 24-HR MAP, 24-hour mean arterial pressure; 24-Hr HR, 24-hour heart rate; Day MAP, daytime mean arterial pressure; Day HR, daytime heart rate; Night MAP, nighttime mean arterial pressure; Night HR, nighttime heart rate; Carotid IMT, carotid intima-media thickness; Carotid AC, carotid arterial compliance; Psv, peak systolic velocity; Pdv, peak diastolic velocity; Pedv, end-diastolic velocity; Pavg, average velocity; VO_{2max}, maximal oxygen uptake. [a]Participants included in N, completed baseline and 6-month data with outliers removed. [b]Values are mean ± SD. [c]All ambulatory measures obtained from participants with 50% successful readings. [d]Clinical resting BP used the average of 2^{nd} and 3^{rd} readings. [e]M2 group used as reference. *clinical significance (p-value between .06-.09); **significant ($p \leq .05$)

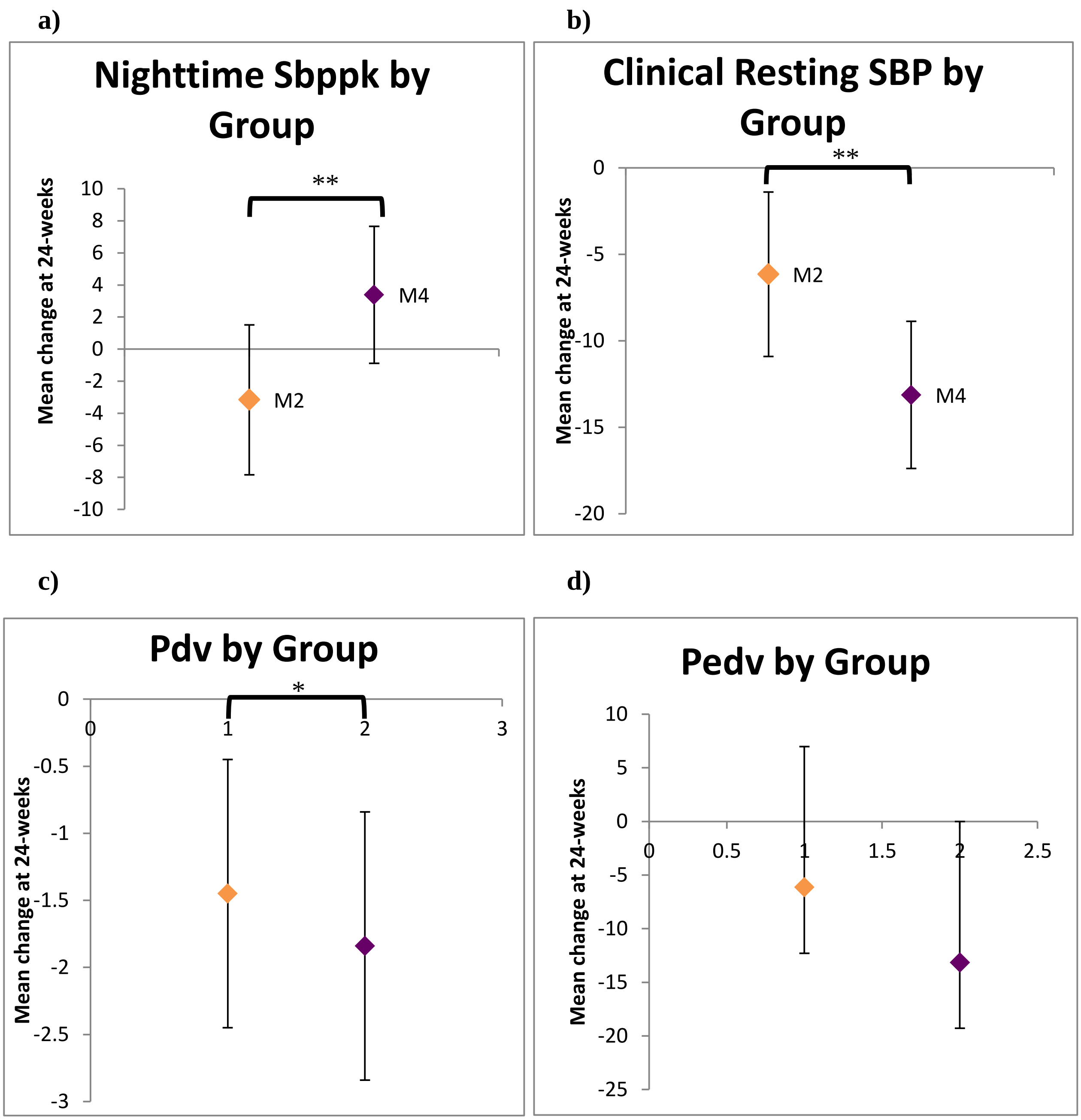


Figure 2: Significant and Clinical Changes after 6 Months between Groups.
Effects of 6 months of M2 and M4 training on: (a) Night sbppk, nighttime peak systolic blood pressure (b) Clinical resting SBP, clinical resting systolic blood pressure; (c) Pdv, peak diastolic velocity; (d) Pedv, end-diastolic velocity. Point estimates and 95%CI (confidence intervals; lower and upper bound) bars presented; *clinical significance (p-value between .06-.09); **significant (p≤.05)

In the analysis with compliant participants (80 %+) included only, results indicate only nighttime peak SBP had a significant decrease between group, which was similar to the findings of the combined compliance and non-compliant participant analyses. The M4 group increased compared to the M2 group which decreased in nighttime peak SBP. Conversely, in the compliant participants' only analysis, the M2 group had a significant positive reduction in carotid IMT compared to the M4 group which increased, see **Table 4** for compliant only participants.

Table 4: CV Outcomes Mean Change Between M2 and M4 with Compliant (80 %+) Participants Only after 6 Months

CV Outcomes	Between Group Differences			
	Estimate Mean Δ	95% Confidence Interval (lower bound, upper bound)		P-value
Ambulatory BP				
24-Hr Systolic BP	-1.83	-6.46	2.91	.43
24-Hr Diastolic BP	.03	-3.44	3.50	.99
24-Hr peak systolic BP	-2.87	-11.03	5.29	.48
24-Hr peak diastolic BP	-5.58	-12.63	1.48	.12
24-Hr MAP	-.93	-3.34	1.49	.44
24-Hr HR	.31	-3.41	4.02	.87
Day Systolic BP	-2.06	-6.84	2.71	.39
Day Diastolic BP	-1.73	-9.59	6.13	.66
Day peak systolic BP	-2.66	-10.26	4.94	.48
Day peak diastolic BP	-2.54	-9.37	4.29	.45
Day MAP	-.98	-4.46	2.50	.57
Day HR	.15	-3,58	3.87	.94
Night systolic BP	-3.03	-10.05	3.99	.39
Night diastolic BP	-1.20	-6.09	3.69	.62
Night peak systolic BP	-11.54	-22.46	-.62	.04**
Night peak diastolic BP	-1.73	-10.00	6.54	.67
Night MAP	.23	-5.88	6.34	.94
Night HR	.51	-3.46	4.49	.79
Clinical Resting BP				
SBP	-.98	-8.69	6.73	.80
DBP	.03	-4.61	4.68	.99
Stiffness and Blood Flow Velocity				
Carotid IMT	-.08	-.15	-.01	.03**
Carotid AC	-.01	-.14	.13	.95
Psv	-3.61	-9.96	2.74	.26
Pdv	-.97	-2.76	.82	.28
Pedv	-1.31	-3.06	.43	.14
Pavg	-1.25	-4.28	1.79	.41
CV Fitness				
VO2max	.50	-2.34	3.34	.72

Abbreviations: Estimate of Δ, estimate of change; BP, blood pressure; Hr, hour; CV, Cardiovascular 24-HR MAP, 24-hour mean arterial pressure; 24-Hr HR, 24-hour heart rate; Day MAP, daytime mean arterial pressure; Day HR, daytime heart rate; Night MAP, nighttime mean arterial pressure; Night HR, nighttime heart rate; Carotid IMT, carotid intima-media thickness; Carotid AC, carotid arterial compliance; Psv, peak systolic velocity; Pdv, peak diastolic velocity; Pedv, end-diastolic velocity; Pavg, average velocity; VO_{2max}, maximal oxygen uptake. [a]Participants included in N, completed baseline and 6-month data with outliers removed. [b]Values are mean ± SD. [c]All ambulatory measures obtained from participants with 50% successful readings. [d]Clinical resting BP used the average of 2nd and 3rd readings. [e]M2 group used as reference. **significant ($p \leq .05$)

4.3 Results within Age by Group

For further analysis, groups were separated and analyzed by "younger" elderly (YE) and "older" elderly (OE) as determined by the data given on age. When stratified by age and group, analyses within YE and within OE between groups revealed different significant CV outcomes. When the YE were analyzed by between group effects, Pedv decreased by an average of 2.17 (95%CI: -4.42, .08; p=.05), however the improvement was seen in the M2 group not in the M4 group, see **Table 5** and **Figure 3**.

The OE group only had a significant change in three ambulatory BP variables: 24-hour HR, daytime HR and nighttime peak SBP. 24-hour HR decreased in both groups however the M2 group further decreased compared to its counterpart. Between group difference for 24-hour HR in the OE revealed a mean difference of -4.86 (95%CI: -9.26, -.47; p=.03). Daytime HR increased in the M4 group compared to the M2 group which decreased. The mean difference in daytime HR for the OE, between groups was -4.84 (95%CI: -9.24, -.44; p=.03). Lastly, nighttime peak SBP decreased in the M2 group but increased in the M4 group. The between group mean difference in nighttime peak SBP for OE was -11.24 (95%CI: -21.13, -1.34; p=.03), see **Table 6** and **Figure 4**.

Table 5: Mean Difference between M2 and M4 for YE Participants after 6 Months

CV Outcome Variable	Younger Elderly			
	Mean Difference	95% Confidence Interval (lower bound, upper bound)		P-Value
Ambulatory BP				
24-Hr Systolic BP	.31	-3.85	4.47	.88
24-Hr Diastolic BP	1.66	-4.77	1.45	.29
24-Hr peak systolic BP	3.19	-3.30	9.69	.32
24-Hr peak diastolic BP	-.32	-6.56	5.92	.92
24-Hr MAP	-.02	-2.85	2.81	.99
24-Hr HR	2.04	-1.52	5.60	.25
Day Systolic BP	-.07	-4.58	4.44	.98
Day Diastolic BP	-.10	-8.26	8.06	.98
Day peak systolic BP	2.95	-3.35	9.25	.35
Day peak diastolic BP	.04	-6.33	6.42	.99
Day MAP	1.52	-1.46	4.51	.31
Day HR	2.03	-1.57	5.62	.26
Night systolic BP	.21	-5.15	5.58	.94
Night diastolic BP	.69	-3.51	4.89	.74
Night peak systolic BP	-.83	-9.63	7.97	.85
Night peak diastolic BP	.72	-7.61	9.06	.86
Night MAP	.93	-3.30	5.16	.66
Night HR	-.87	-4.27	2.53	.60
Clinical Resting BP				
SBP	8.00	-1.28	17.28	.09*
DBP	3.79	-1.12	8.69	.13
Arterial Stiffness and Blood Flow Velocity				
Carotid IMT	-.04	-.09	.02	.18
Carotid AC	.13	-.02	.28	.09*
Psv	-4.49	-10.93	1.95	.17
Pdv	-2.17	-4.42	.08	.058
Pedv	-2.29	-4.56	-.01	.05**
Pavg	-3.19	-6.63	.24	.06*
CV Fitness				
VO2max	-.27	-3.02	2.49	.85

Abbreviations: Estimate of Δ, estimate of change; BP, blood pressure; Hr, hour; CV, Cardiovascular 24-HR MAP, 24-hour mean arterial pressure; 24-Hr HR, 24-hour heart rate; Day MAP, daytime mean arterial pressure; Day HR, daytime heart rate; Night MAP, nighttime mean arterial pressure; Night HR, nighttime heart rate; Carotid IMT, carotid intima-media thickness; Carotid AC, carotid arterial compliance; Psv, peak systolic velocity; Pdv, peak diastolic velocity; Pedv, end-diastolic velocity; Pavg, average velocity; VO_{2max}, maximal oxygen uptake. [a]Participants included in N, completed baseline and 6-month data with outliers removed. [b]Values are mean ± SD. [c]All ambulatory measures obtained from participants with 50% successful readings. [d]Clinical resting BP used the average of 2nd and 3rd readings. [e]M2 group used as reference. *clinical significance (p-value between .06-.09); **significant (p≤.05)

Table 6: Mean Difference between M2 and M4 for OE Participants after 6 Months

CV Outcome Variable	Older Elderly			
	Mean Difference	**95% Confidence Interval (lower bound, upper bound)**		**P-Value**
Ambulatory BP				
24-Hr Systolic BP	-.41	-6.71	5.89	.90
24-Hr Diastolic BP	-.54	-3.93	2.84	.75
24-Hr peak systolic BP	-5.60	-13.29	2.08	.15
24-Hr peak diastolic BP	-3.12	-10.01	3.78	.36
24-Hr MAP	-.47	-4.15	3.20	.79
24-Hr HR	-4.86	-9.26	-.47	.03**
Day Systolic BP	.72	-4.55	5.99	.78
Day Diastolic BP	-3.20	-11.52	5.12	.44
Day peak systolic BP	-2.79	-10.06	4.49	.44
Day peak diastolic BP	-1.44	-7.59	4.70	.63
Day MAP	-1.76	-6.58	3.06	.46
Day HR	-4.84	-9.24	-.44	.03**
Night systolic BP	-3.30	-11.53	4.93	.42
Night diastolic BP	.70	-3.67	5.08	.74
Night peak systolic BP	-11.24	-21.13	-1.34	.03**
Night peak diastolic BP	-.88	-7.26	5.50	.78
Night MAP	2.87	-2.68	8.42	.30
Night HR	-2.37	-7.40	2.66	.34
Clinical Resting BP				
SBP	6.86	-3.16	16.88	.17
DBP	2.87	-2.89	8.64	.32
Arterial Stiffness and Blood Flow Velocity				
Carotid IMT	-.04	-.13	.05	.40
Carotid AC	-.04	-.20	.12	.63
Psv	-2.40	-10.15	5.34	.53
Pdv	-.41	-2.41	1.59	.68
Pedv	-.28	-1.87	1.32	.72
Pavg	-.60	-4.22	3.02	.74
CV Fitness				
VO2max	.97	-2.38	4.32	.56

Abbreviations: Estimate of Δ, estimate of change; BP, blood pressure; Hr, hour; CV, Cardiovascular 24-HR MAP, 24-hour mean arterial pressure; 24-Hr HR, 24-hour heart rate; Day MAP, daytime mean arterial pressure; Day HR, daytime heart rate; Night MAP, nighttime mean arterial pressure; Night HR, nighttime heart rate; Carotid IMT, carotid intima-media thickness; Carotid AC, carotid arterial compliance; Psv, peak systolic velocity; Pdv, peak diastolic velocity; Pedv, end-diastolic velocity; Pavg, average velocity; VO_{2max}, maximal oxygen uptake. [a]Participants included in N, completed baseline and 6-month data with outliers removed. [b]Values are mean ± SD. [c]All ambulatory measures obtained from participants with 50% successful readings. [d]Clinical resting BP used the average of 2nd and 3rd readings. [e]M2 group used as reference. **significant ($p \leq .05$)

a)

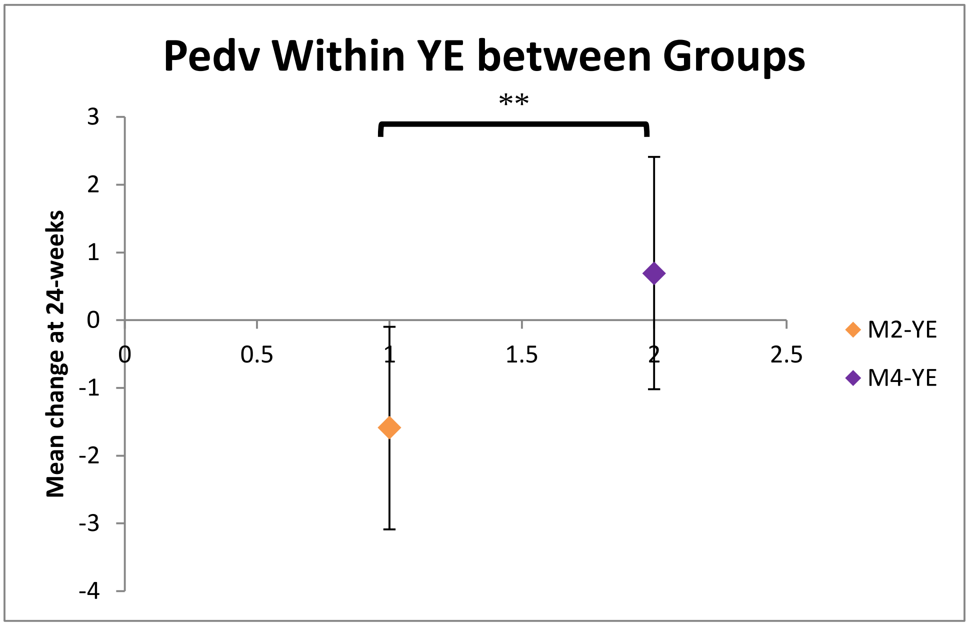
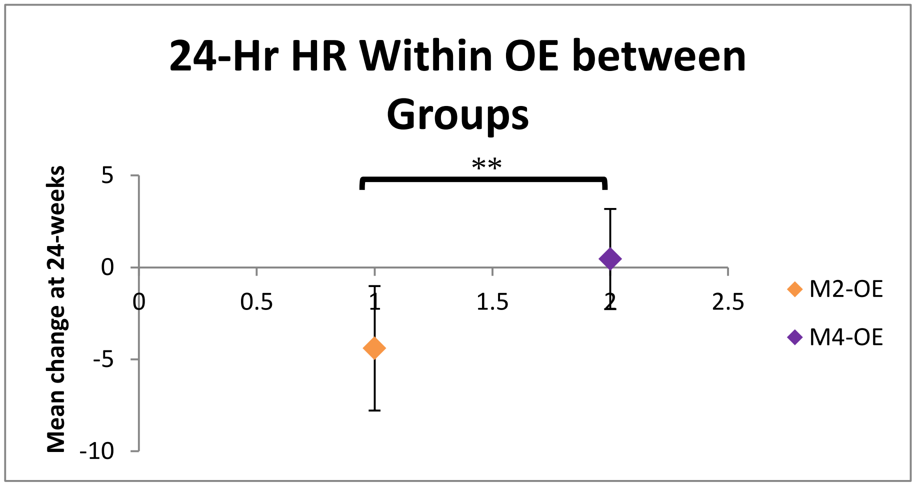


Figure 3 – YE Significant Outcomes in End-Diastolic Blood Flow Velocity between Groups. Effects of 6 months of M2 and M4 training on: (a) Pedv, end-diastolic velocity. Point estimates and 95%CI (confidence interval; lower and upper) bars presented; **significant ($p \leq .05$).

a)



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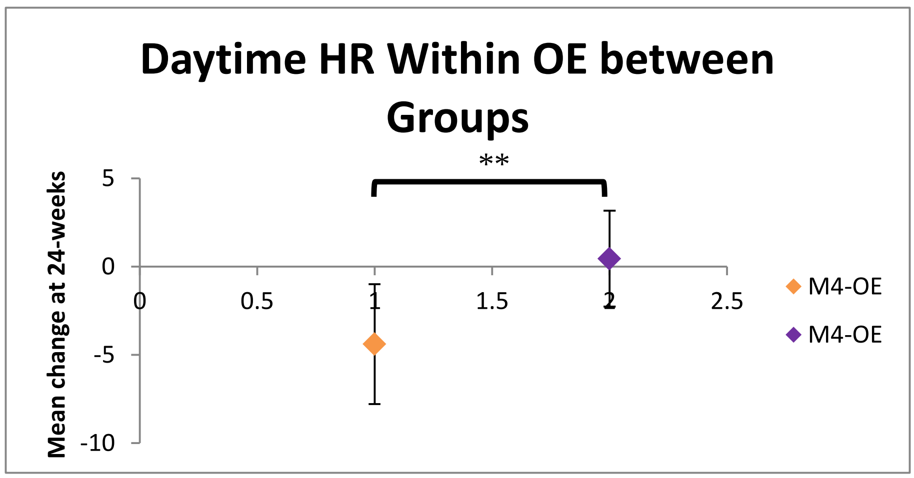

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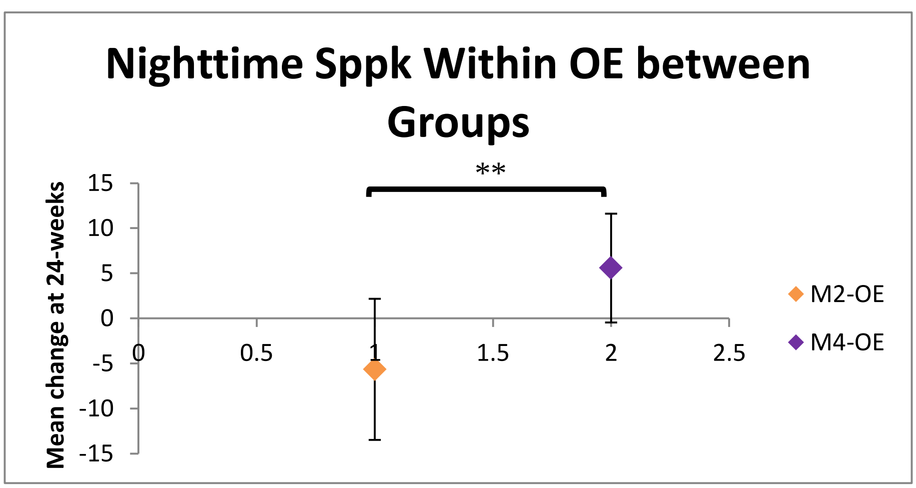


Figure 4 – OE Significant Outcomes in Ambulatory BP between Groups. Effects of 6 months of M2 and M4 training on: (a) 24-Hr HR, 24-hour hear rate; (b) Day HR, daytime heart rate; (c) Night Sbppk, nighttime peak systolic blood pressure**.** Point estimates and 95%CI (confidence intervals; lower and upper) bars presented; **significant (p≤.05)

4.4 Results by Sex

Additional analyses were completed based on sex and group to see whether one sex improved over the other. Both males and females differed on which CV variables changed significantly.

Males only significantly changed in nighttime HR. The M4 group increased in night HR compared to the M2 group which decreased. Mean difference between groups was -7.36 (95%CI: -13.05, -1.66; p= .01), see **Table 7** and **Figure 5**.

Conversely, females significantly changed in nighttime peak SBP clinical resting DBP and end-diastolic velocity. Nighttime peak SBP increased in the M4 group compared to the M2 group which decreased. Female nighttime peak SBP had a mean group difference of -7.34 (95%CI: -14.36, -.32). Clinical resting DBP had a greater decrease in the M4 group compared to the M2 group with a between groups mean change of 4.20 (95%CI: .09, 8.31; p=.05). End-Diastolic velocity within females increased in the M4 group compared to the M2 group which decreased. Mean difference for females between groups was -1.65 (95%CI: -3.31, .01; p=.05), see **Table 8** and **Figure 6**.

Table 7: Mean Difference between M2 and M4 for Males Only Participants between groups after 6 Months

CV Outcome Variables	Males			
	Mean Difference	**95% Confidence Interval (lower bound, upper bound)**		**P-Value**
Ambulatory BP				
24-Hr Systolic BP	-2.79	-12.54	6.95	.55
24-Hr Diastolic BP	-2.31	-7.41	2.79	.35
24-Hr peak systolic BP	-1.94	-12.74	8.86	.71
24-Hr peak diastolic BP	-3.93	-13.43	5.58	.40
24-Hr MAP	-2.52	-7.57	2.52	.31
24-Hr HR	-5.08	-10.79	.63	.08*
Day Systolic BP	-1.32	-8.59	5.95	.71
Day Diastolic BP	-6.00	-16.34	4.32	.24
Day peak systolic BP	-2.70	-12.97	7.58	.59
Day peak diastolic BP	-4.70	-13.46	4.06	.27
Day MAP	-2.90	-9.51	3.72	.37
Day HR	-5.06	-10.78	.65	.08*
Night systolic BP	-5.78	-16.85	5.30	.29
Night diastolic BP	-1.66	-9.13	5.81	.65
Night peak systolic BP	-4.56	-19.57	10.46	.53
Night peak diastolic BP	-1.97	-12.21	8.27	.69
Night MAP	-1.17	-7.75	5.40	.71
Night HR	-7.36	-13.05	-1.66	.01**
Clinical Resting BP				
SBP	11.32	-4.09	26.74	.14
DBP	1.93	-5.86	9.74	.61
Arterial Stiffness and Blood Flow Velocity				
Carotid IMT	-.03	-.13	.07	.51
Carotid AC	.13	-.10	.36	.25
Psv	-1.31	-11.52	8.90	.79
Pdv	-1.00	-4.04	2.04	.50
Pedv	-.34	-3.10	2.42	.80
Pavg	-1.27	-6.53	3.99	.62
CV Fitness				
VO2max	..23	-4.01	4.48	.91

Abbreviations: Estimate of Δ, estimate of change; BP, blood pressure; Hr, hour; CV, Cardiovascular 24-HR MAP, 24-hour mean arterial pressure; 24-Hr HR, 24-hour heart rate; Day MAP, daytime mean arterial pressure; Day HR, daytime heart rate; Night MAP, nighttime mean arterial pressure; Night HR, nighttime heart rate; Carotid IMT, carotid intima-media thickness; Carotid AC, carotid arterial compliance; Psv, peak systolic velocity; Pdv, peak diastolic velocity; Pedv, end-diastolic velocity; Pavg, average velocity; VO_{2max}, maximal oxygen uptake. [a]Participants included in N, completed baseline and 6-month data with outliers removed. [b]Values are mean ± SD. [c]All ambulatory measures obtained from participants with 50% successful readings. [d]Clinical resting BP used the average of 2nd and 3rd readings. [e]M2 group used as reference. *clinical significance (p-value between .06-.09); **significant ($p \leq .05$)

Table 8: Mean Difference between M2 and M4 for Females Only Participants between groups after 6 Months

CV Outcome Variables	Females			
	Mean Difference	95% CI		P-Value
Ambulatory BP				
24-Hr Systolic BP	.55	-3.02	4.12	.76
24-Hr Diastolic BP	1.15	-1.39	3.70	.37
24-Hr peak systolic BP	-1.14	-6.99	4.72	.70
24-Hr peak diastolic BP	-1.35	-6.43	3.73	.59
24-Hr MAP	.04	-2.35	2.43	.98
24-Hr HR	.59	-2.43	3.60	.70
Day Systolic BP	-.05	-4.01	3.92	.98
Day Diastolic BP	1.17	-5.85	8.19	.74
Day peak systolic BP	.94	-4.48	6.37	.73
Day peak diastolic BP	.51	-4.38	5.39	.84
Day MAP	.60	-2.05	3.24	.65
Day HR	.44	-2.66	3.55	.78
Night systolic BP	-.16	-5.09	4.76	.95
Night diastolic BP	1.50	-1.52	4.53	.32
Night peak systolic BP	-7.34	-14.36	-.32	.04**
Night peak diastolic BP	.94	-4.90	6.77	.75
Night MAP	2.47	-1.38	6.32	.20
Night HR	.78	-2.30	3.85	.61
Clinical Resting BP				
SBP	3.99	-3.17	11.15	.27
DBP	4.20	.09	8.31	.05**
Arterial Stiffness				
Carotid IMT	-.03	-.10	.04	.40
Carotid AC	.05	-.05	.15	.32
Psv	-3.70	-9.11	1.71	.18
Pdv	-1.42	-3.16	.32	.11
Pedv	-1.65	-3.31	.01	.05**
Pavg	-2.18	-4.92	.56	.12
CV Fitness				
VO2max	.48	-1.81	2.78	.67

Abbreviations: Estimate of Δ, estimate of change; BP, blood pressure; Hr, hour; CV, Cardiovascular 24-HR MAP, 24-hour mean arterial pressure; 24-Hr HR, 24-hour heart rate; Day MAP, daytime mean arterial pressure; Day HR, daytime heart rate; Night MAP, nighttime mean arterial pressure; Night HR, nighttime heart rate; Carotid IMT, carotid intima-media thickness; Carotid AC, carotid arterial compliance; Psv, peak systolic velocity; Pdv, peak diastolic velocity; Pedv, end-diastolic velocity; Pavg, average velocity; VO_{2max}, maximal oxygen uptake. [a]Participants included in N, completed baseline and 6-month data with outliers removed. [b]Values are mean ± SD. [c]All ambulatory measures obtained from participants with 50% successful readings. [d]Clinical resting BP used the average of 2^{nd} and 3^{rd} readings. [e]M2 group used as reference. *clinical significance (p-value between .06-.09); **significant ($p \leq .05$)

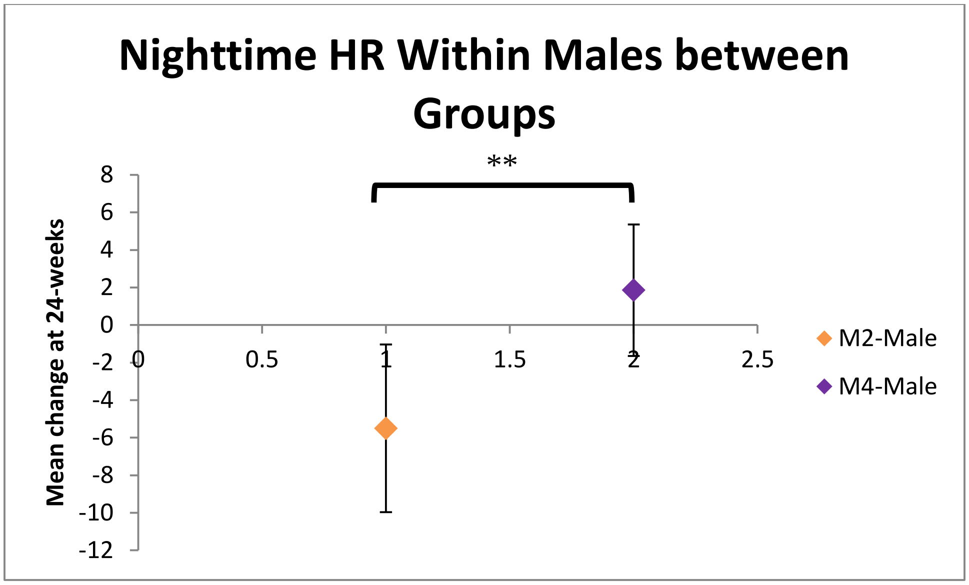
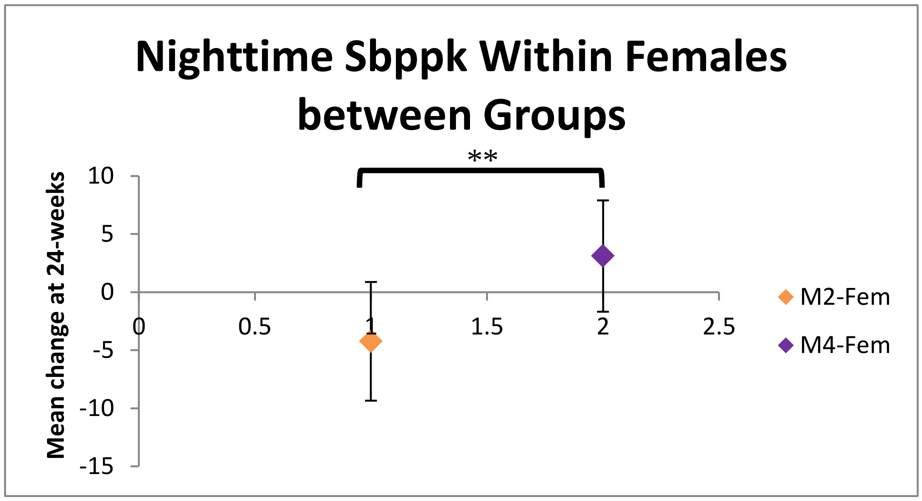


Figure 5 – Males Significant Outcomes in Ambulatory BP between Groups. Effects of 6 months of M2 and M4 training on: (a) Night HR, nighttime heart rate; (b) 24-Hr HR, 24-hour heart rate; (c) Day HR, daytime heart rate. Point estimates and 95%CI (confidence interval; lower and upper) bars presented; **significant ($p \leq .05$)

a)



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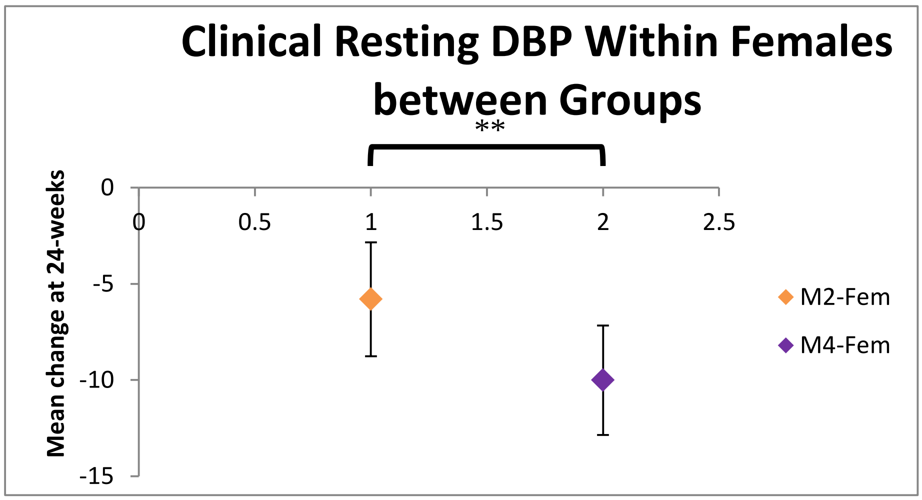

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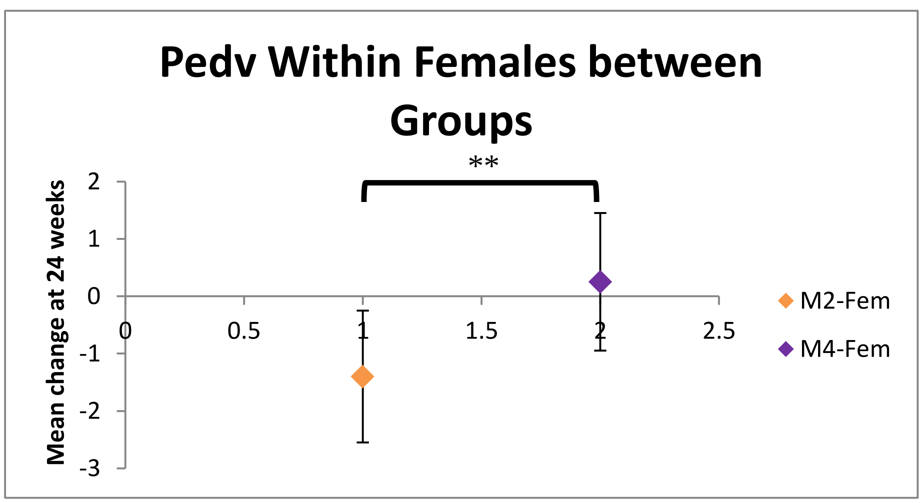

Figure 6 – Females Significant CV Outcomes between Groups. Effects of 6 months of M2 and M4 training on: (a) Night Sbppk, nighttime peak systolic blood pressure; (b) Clinical resting DBP, clinical resting diastolic blood pressure average readings of 2 and 3; (c) Pedv, end-diastolic velocity. Point estimates and 95%CI (confidence interval; lower and upper) bars presented; **significant (p≤.05)

Correlation Analyses

Correlation analyses were conducted at baseline and at 6 months to determine whether the intervention was strengthened or diminished between two variables that were correlated.

Bivariate correlation analyses were conducted between 24-hour ambulatory BP variables and AC at both baseline and at 6-months. Analyses revealed no strong positive or negative relationships at baseline, except for a positive weak relationship between AC and 24-hour SBP ($r=.22$; $p=.05$), and a negative weak relationship between AC and 24-hour HR ($r=-.25$; $p=.02$). At 6-months the relationship between AC and 24-hour HR changed to a strong negative relationship ($r= -.05$; $p\leq.01$). The remaining variables were all negligible or weak relationships.

Further correlation analyses were performed between AC, age and BMI. Analyses revealed at baseline, a weak negative correlation between age and AC at baseline ($r=-.02$; $p=.83$), after 6-months the relationship was weaker ($r=-.12$; $p=.31$). AC and BMI were negligible, however at 6-months, a weak positive relationship was observed ($r=.24$; $p=.04$). See Appendix C for correlation analyses.

Adverse Events

Eight participants suffered an adverse event during the 6-month intervention period. Of the eight, half of the participants endured an adverse event during the exercise class. The first participant did not suffer any injuries, but found their HR was too high during the exercise, and felt a pounding sensation in their chest. The participant walked for 15 mins to cool down, and rejoined the class once they felt better. The second participant felt lightheaded after the strength exercise component. The participant sat down and rested until they felt better. The third participant felt a sudden pain on the lateral side above their knee. Exercises were modified to accommodate the knee pain. The last participant fainted, lost their balance and hit their elbow on the wall during stretching at the end of the class. Participant got back up and felt fine afterwards. Similarly, another participant suffered blurred vision and dizziness; however they felt this way prior to exercise class. Another participant suffered from chronic back pain and it worsened; uncertain of whether it was exercise class related or not. One participant did not suffer any injuries during the exercise class, but had personal medical issues which required placement of 3 stents. The participant rejoined the class once recovered. The final participant had a pinched nerve with leg and back soreness. Pain was amplified during exercise class.

Chapter 7: Summary and Conclusion

Collective evidence has proposed the aging brain as acquiescent to neuronal and cognitive plasticity[104]. Older adults are primarily affected by the decline in cognitive domains including memory, language and executive function which are all associated with dementia and therefore require critical attention to the prevention and maintenance of brain function[105,106].

Contributing factors to vascular health such as diet and physical inactivity play a role in the effects of vascular however; blood pressure and arterial health are the single most detectable risk factor for dementia excluding age, and the only treatable risk factor to date[26]. Although studies have successfully looked at the use of aerobic exercise to prevent and reduce high blood pressure and arterial stiffness in order to promote brain health in older adults, the underlying mechanisms are still unclear[107].

The current study is the first prospective, 6-month, randomized controlled trial in a community-dwelling older adult population with subjective memory complaints, which examines the effects of a multiple modality mind-motor (M4) exercise program on 24-hour ambulatory and clinical resting BP, compared to a multiple modality (M2) exercise program alone. This investigation is notable, as examining the influence of M4 on BP and other related CV outcomes within this population is important. Furthering our knowledge of potential ways to mediate and support BP reductions and its advancement may improve cognitive function and overall risk of CVD within the older adult population.

Effects of M2 and M4 on ambulatory BP and clinical resting SBP and DBP

For the ambulatory BP outcomes, there were no differences between groups except for nighttime peak SBP where a significant change was found, with the M2 group decreasing in peak nighttime SBP compared to the M4 group. The decrease in peak nighttime SBP can aid in the effect of nocturnal dipping, by which nighttime BP should be 10-15% lower than daytime BP[108]. The absence of nocturnal dipping and heightened surge of BP during the daytime can lead to specific organ damage and augmented CVD risk, including CVD morbidity and mortality[109-112].

On the contrary, the M4 group decreased considerably more compared to the M2 group in clinical resting SBP. This also coincides with the findings of Corneilissen et al., who assessed office blood pressure after 10 weeks of either lower or higher intensity training in adults (age averaged 59 years). Both types of training reduced office BP, however the higher intensity training reduced SBP even further than the lower intensity training group[112].

By age and group, within the YE between groups, no significant changes were found in any BP measures. Within sex and between groups, both M2 and M4 females decreased in clinical resting DBP however the M4 females declined much further.

Conversely, within the OE between groups, 24-hour HR decreased in the M2-OE group compared to the M4-OE group which had an increase in 24-hour HR. Furthermore, these findings in 24-hour HR were replicated in daytime HR and nighttime peak SBP. The Framingham Heart Study (longitudinal cohort study) followed subjects for 30 years and discovered a continuous increase in SBP between the ages of 30 and 84 years or more.

However, DBP has a more variable configuration with age, whereby DBP increases until the age of 50, and slowly decreases from 60 years onwards, resulting in a steep incline in pulse pressure with aging[11]. Vasan et al., disturbingly re-counted from the Framingham Heart Study that 90% of participants, men and women in their mid to late-life were probable to develop hypertension onwards throughout the rest of their life[113]. Therefore, growing evidence has shown the importance of controlling for nighttime BP can greatly affect the risk of CVD and aging.

When stratified by sex, within the males in the M2 group, a significant decrease in nighttime HR in comparison to the M4 males whose nighttime HR increased. Alternatively, females in the M2 group significantly decreased in nighttime peak SBP compared to the M4 females who increased in nighttime peak SBP. Sierra et al., found after monitoring 24-hour ambulatory blood pressure, those with a non-dipping profile were older and often obese women who suffered long-term hypertension, previous diagnosis of dyslipidemia, Type 2 Diabetes or CVD[114]. However, within the current study, nocturnal dipping was not accounted for and should be observed in future studies as it plays a vital role as we age and between sex.

In general, M2 and M4 groups both improved in certain variables of ambulatory and clinical resting BP, which help decrease the risk of CVD. Furthermore, Beason-Held et al., found an association between hypertension and dementia occurrence, whereby studies have found hypertension with operating brain measures linked to cerebral blood flow[115]. Positron emission tomography (PET) data collected on participants with hypertension (140/90 mm hg) identified with a decline in regional cerebral blood flow over time in several cortical regions, including the prefrontal cortex and anterior cingulate cortex compared to participants without hypertension. This suggests brain areas responsible for attention and executive function are susceptible to the influences of vascular risk factors such as hypertension[3]. However limitations do exist as the study did not assess other vascular function i.e. cardiac output, endothelial functions or atherosclerotic load which could suggest participants with hypertension may not be the sole cause for reducing regional cerebral blood flow, but other vascular risk factors that participants may suffer from could also contribute to the reduction in regional cerebral blood flow[3]. Furthermore, cross-sectional longitudinal studies have shown a positive correlation between hypertension and cognitive decline, whereby subjects who suffered from hypertension performed much worse on mental status examinations[4]. Elevated systolic pressures in untreated hypertensive, cognitively normal subjects (mean age, 61.3 years) reduced grey matter volumes in different areas of the brain[116], and mid-life hypertension was associated with a decline in hippocampal volume after a 30 year follow-up[7], suggesting hypertension can alter the brain structurally leading to abnormalities in cognitive function[117]. Therefore, control for blood pressure subsequently affects not only CVD risk, but structural and functional brain alterations. However duration of treatment or chronicity of hypertension was not documented, although majority (84%) of participants were diagnosed with hypertension for over 10 years, consequently detecting the effect of long-term hypertension on the central nervous system[117]. Better control of blood pressure is indicative of the prevention of dementia in late-life.

Although the current study lacked in number of significant changes in BP, more than half of our participants were diagnosed as hypertensive of which only 31 individuals were taking medication. However, their regional cerebral blood flow was not monitored; perhaps not many changes in BP occurred because structurally their brain had already been altered, to the extent that treating blood pressure could not reverse the effects. Therefore, monitoring regional cerebral blood flow in conjunction with BP and its possible predictive pathway for dementia could elucidate the appropriate method of prevention of hypertension and other vascular risk factors[117].

Additionally, the current investigation was part of a larger-scale study of which biological determinants of exercise and cognition are to be explored in further detail. Though it is known CV health does play a role in cognition and exercise can improve CV health, the influence of CV health on cognition still requires further research.

Effects of M2 and M4 on carotid arterial stiffness, blood flow velocity and CV fitness

Neither M2 nor M4 had any significant influence on carotid arterial stiffness (AC and IMT), blood flow velocity or CV fitness. It is possible that increasing IMT with age may be due to external exposures to risk factors that were not disclosed or known[118].

When further stratified by age, YE improved only in blood flow velocity, of which only Pedv had a significant change between M2 and M4. M4-YE had increased in Pedv compared to the M2-YE which decreased. Within the OE between groups, no significant changes were found in carotid arterial stiffness, blood flow velocity or CV fitness. It was determined by Ahzim et al., that an age-associated decline in blood flow velocities in the common carotid artery was altered and improved in those who were healthy, middle-aged or older who performed habitual aerobic exercise [119]. However with reference to this study, improved blood flow velocities of the common carotid artery was only found in the M4 group and in the YE group when further stratified, regardless of health or habitual exercise.

The only significance found by sex was a significant change of Pedv in females. The M4 females had an increase in Pedv whereas the M2 females decreased in Pedv. This contradicts the observations by Denarie et al., who did not observe changes in pulse wave velocity but rather found a trend in lowering IMT in women than in men on both sides of the carotid artery and at different ages; however they found middle-aged adults on the left side to have a statistically significant decrease in IMT[118]. Though, the fact there was no significant changes in our study population could attribute to age-related arterial hypertrophy in both sexes[118]. Yet, sex differences in carotid artery dimensions still remain unclear.

CV fitness was not significantly altered when observed by group, within age-between groups or within sex-between groups. This was contradictive to studies including Linde et al., and Fabre et al., who found improvement in VO2max for almost all of their intervention variables except for one (mental training + aerobic training) in the study by Fabre et al. Furthermore, they found an increase in their control groups as well[22,69].

Correlation Analyses

Correlations between AC and blood pressure remained weak or negligible except for AC and 24-hour HR which had a strong negative relationship. However, systolic and diastolic BP were both highly correlated with their peak BP counterparts for all three time frames (24 hours, daytime and nighttime) at baseline. After 6 months, relationships remained strongly correlated to one another. Analyses regarding AC, age and BMI revealed only weak correlations both at baseline and at 6-months.

These correlations are were not very comparable to the findings by Iannuzzi et al., by which correlations among age, systolic blood pressure, and BMI were positively correlated with external and internal common carotid diameters[120].

7.1 Study Limitations

The results of the current study are novel and meaningful, however, limitations do exist. A limitation of the present study is the data used for ambulatory blood pressure measures. Some participants only had the minimum amount of readings (20/40 readings) with very few nighttime readings, which could skew the data. Therefore, these results should be interpreted with caution. Although a diary was given to the participant to record any events that may elevate their blood pressure, some participants may have changed their regular routine as a consequence of wearing the monitor for the 24-hours, therefore readings could be inaccurate. Another factor that may or may not have been recorded that also play a role in the effect of BP, which were not accounted for included anxiety, a consequence of the sympathetic nervous system (SNS) influenced by the emotional state[121]. A chronic level of anxiety in a person has been identified to be an association between environmental stress and cardiovascular responses that may arbitrate the formation of or contribute to chronic hypertension[122].

A limitation was also found in the ultrasound measurement of the common carotid arterial wall by which discrepancies in the measurement could have occurred. On occasion, arterial wall imaging can be unclear on the ultrasound monitor, or the endothelial layer may not be clearly defined, resulting in subjective measurements, which may not be as accurate. Although inter-intra reliability was conducted, it was not reported due to greater than average discrepancies in arterial diameters within a participant. The discrepancies lie in the movement of the cursor, where a mere single movement of the cursor can change the measurement by one- tenths of a millimeter consequently increasing the variability in measurements.

Moreover, ultrasound images were not recorded to allow revisions of the artery and ensure accurate measurements were taken. Furthermore, not measuring both left and right sides of the carotid artery can also impact results, as they tend to differ over age[118]. Although Denarie et al., also found unknown differences between the right and left, the anatomical position of each artery is different. The left common carotid artery is directly branched on the aorta whereas the right common carotid results from the division of the brachiocephalic trunk. Therefore, it is possible to have differences in arterial growth between both arteries[118].

Another limitation was that several participants were under treatment for various medications, which could also influence the results. Although BP, cardiovascular and other related medications were noted, they were only monitored at the beginning and end of the intervention. Some participants in the study had untreated high BP, cholesterol, and diabetes, which could also impact the results of the current investigation. Likewise, interactions with other medications could have also interfered with the results. In addition, reporting bias of medication, medical history and cognitive complaint could also be a factor. Some individuals may have said ‘yes’ to having a cognitive complaint but did not actually have any concerns with their memory. Jessen et al., relayed his concern of how to conceptualize having a subjective cognitive complaint and determined a more accurate way of identifying the at risk population of cognitive decline[123]. Although we asked our participants if they had a subjective cognitive complaint, we did not ask them whether or not they were concerned which would determine whether they were at risk for cognitive decline in combination with observing AD biomarkers (i.e. brain anatomy including glucose metabolism[124], amyloid deposition[125]; cerebral spinal fluid markers including Aß42[126]) that could help identify the preclinical stage of cognitive decline, according to Jessen and colleagues.

Additionally, the current study may be under powered as we only had a total of 89 participants of which less than half were compliant (80% or more attendance) with the exercise class. Therefore, the lack of changes between group, age and group, and sex and group could be attributed to the undersized population which affected the statistical power of the study. While stratifying by age and by sex is important, it may not be the best way to accurately observe results. Shimzu et al., suggested stratifying by functional mobility may be more important than looking between age and sex because an individual's mobility would have an impact on how strenuous an exercise they can handle[59]. Furthermore, some participants may not have reached their target HR each class, and therefore did not receive the optimal training to better improve CV health. This could also raise the question whether the prescribed exercises were enough to observe a change in vascular health.

Lastly, our study population was predominantly Caucasian, which does not necessarily reflect the population of older adults at large. Therefore, future studies should consider more ethnic groups in their population.

7.2 Perspectives

As we age, the prevalence of cognitive impairment increases with age and the incidence of individuals displaying some form of cognitive impairment prior to meeting any diagnostic criteria for dementia (i.e., mild cognitive impairment; MCI, or cognitive impairment not dementia; CIND) is doubled, compared to Alzheimer's disease and related dementias[127]. Therefore, it is imperative to look at older adults who have self-reported claims of poorer cognition regardless of having an actual indication of cognitive impairment to better control the incidence of dementia in later-life[128-131].

Furthermore, CVD risk factors such as hypertension and arterial stiffness are also on the rise as we age, and have been confirmed as a contributing factor towards dementia and its progression to Alzheimer's Disease[64,132]. An editorial in the Journal of the American Medical Association states the most readily modifiable risk factors of dementia are vascular risk factors. Front-line prevention measures and treatment strategies for CVD risk factors include lifestyle modifications such as incorporating habitual, moderate to vigorous aerobic exercise[133]. Aerobic exercise has been proven to mitigate CVD risk factors by reducing BP[133,134] and arterial stiffness in older adults[48].

Previous research has also found aerobic exercise improved CVD risk factors and cognitive function, specifically executive function in healthy older adults and those with cognitive impairment[20,134-137], demonstrating the association between CVD risk factors and cognition. Increases in cardiovascular fitness enhanced important regions of the brain including the attentional network[134]; however, the neural mechanisms responsible for enhancement in cognition due to improved CVD risk factors in aging adults have not been fully investigated[134]. Additionally, cognitive training has also been shown to improve executive function and memory in healthy older adults and in cognitively impaired older adults[21,50].

Due to the observed fixed association between cognition and vascular health[20,134-137], the use of cognitive training to improve vascular health the current study incorporated a multiple modality and mind-motor training program to see whether both prescriptions given together would benefit CVD risk factors, in turn improving cognition in older adults. In addition, elucidating the optimal regimen for preserving CVD risk factors and cognition.

This study conducted a larger-scale randomized controlled trial of community-dwelling older adults who have a subjective memory complaint and found some evidence of a beneficial impact from a multiple modality mind-motor program on CV health. However future research should look at nocturnal dipping and cerebral blood flow as outcome measures to understand physiologically, the CV mechanisms within the brain. More ethnic groups should also be included to better generalize the findings of the intervention in an older adult population. Furthermore, better control of external factors such as anxiety and stratifying by physical function levels should be further investigated when looking at a combined aerobic and cognitive training exercise program on vascular health.

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Appendix A: Chapter 1 Figures

PEDro scale

1.	eligibility criteria were specified	no □	yes □	where:
2.	subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	no □	yes □	where:
3.	allocation was concealed	no □	yes □	where:
4.	the groups were similar at baseline regarding the most important prognostic indicators	no □	yes □	where:
5.	there was blinding of all subjects	no □	yes □	where:
6.	there was blinding of all therapists who administered the therapy	no □	yes □	where:
7.	there was blinding of all assessors who measured at least one key outcome	no □	yes □	where:
8.	measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	no □	yes □	where:
9.	all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	no □	yes □	where:
10.	the results of between-group statistical comparisons are reported for at least one key outcome	no □	yes □	where:
11.	the study provides both point measures and measures of variability for at least one key outcome	no □	yes □	where:

The PEDro scale is based on the Delphi list developed by Verhagen and colleagues at the Department of Epidemiology, University of Maastricht (*Verhagen AP et al (1998). The Delphi list: a criteria list for quality assessment of randomised clinical trials for conducting systematic reviews developed by Delphi consensus. Journal of Clinical Epidemiology, 51(12):1235-41*). The list is based on "expert consensus" not, for the most part, on empirical data. Two additional items not on the Delphi list (PEDro scale items 8 and 10) have been included in the PEDro scale. As more empirical data comes to hand it may become possible to "weight" scale items so that the PEDro score reflects the importance of individual scale items.

The purpose of the PEDro scale is to help the users of the PEDro database rapidly identify which of the known or suspected randomised clinical trials (ie RCTs or CCTs) archived on the PEDro database are likely to be internally valid (criteria 2-9), and could have sufficient statistical information to make their results interpretable (criteria 10-11). An additional criterion (criterion 1) that relates to the external validity (or "generalisability" or "applicability" of the trial) has been retained so that the Delphi list is complete, but this criterion will not be used to calculate the PEDro score reported on the PEDro web site.

The PEDro scale should not be used as a measure of the "validity" of a study's conclusions. In particular, we caution users of the PEDro scale that studies which show significant treatment effects and which score highly on the PEDro scale do not necessarily provide evidence that the treatment is clinically useful. Additional considerations include whether the treatment effect was big enough to be clinically worthwhile, whether the positive effects of the treatment outweigh its negative effects, and the cost-effectiveness of the treatment. The scale should not be used to compare the "quality" of trials performed in different areas of therapy, primarily because it is not possible to satisfy all scale items in some areas of physiotherapy practice.

Last amended June 21st, 1999

Appendix A. Figure 1: PEDro Scale Item description and Scoring

Notes on administration of the PEDro scale:

All criteria	**Points are only awarded when a criterion is clearly satisfied**. If on a literal reading of the trial report it is possible that a criterion was not satisfied, a point should not be awarded for that criterion.
Criterion 1	This criterion is satisfied if the report describes the source of subjects and a list of criteria used to determine who was eligible to participate in the study.
Criterion 2	A study is considered to have used random allocation if the report states that allocation was random. The precise method of randomisation need not be specified. Procedures such as coin-tossing and dice-rolling should be considered random. Quasi-randomisation allocation procedures such as allocation by hospital record number or birth date, or alternation, do not satisfy this criterion.
Criterion 3	*Concealed allocation* means that the person who determined if a subject was eligible for inclusion in the trial was unaware, when this decision was made, of which group the subject would be allocated to. A point is awarded for this criteria, even if it is not stated that allocation was concealed, when the report states that allocation was by sealed opaque envelopes or that allocation involved contacting the holder of the allocation schedule who was "off-site".
Criterion 4	At a minimum, in studies of therapeutic interventions, the report must describe at least one measure of the severity of the condition being treated and at least one (different) key outcome measure at baseline. The rater must be satisfied that the groups' outcomes would not be expected to differ, on the basis of baseline differences in prognostic variables alone, by a clinically significant amount. This criterion is satisfied even if only baseline data of study completers are presented.
Criteria 4, 7-11	*Key outcomes* are those outcomes which provide the primary measure of the effectiveness (or lack of effectiveness) of the therapy. In most studies, more than one variable is used as an outcome measure.
Criterion 5-7	*Blinding* means the person in question (subject, therapist or assessor) did not know which group the subject had been allocated to. In addition, subjects and therapists are only considered to be "blind" if it could be expected that they would have been unable to distinguish between the treatments applied to different groups. In trials in which key outcomes are self-reported (eg, visual analogue scale, pain diary), the assessor is considered to be blind if the subject was blind.
Criterion 8	This criterion is only satisfied if the report explicitly states *both* the number of subjects initially allocated to groups *and* the number of subjects from whom key outcome measures were obtained. In trials in which outcomes are measured at several points in time, a key outcome must have been measured in more than 85% of subjects at one of those points in time.
Criterion 9	An *intention to treat* analysis means that, where subjects did not receive treatment (or the control condition) as allocated, and where measures of outcomes were available, the analysis was performed as if subjects received the treatment (or control condition) they were allocated to. This criterion is satisfied, even if there is no mention of analysis by intention to treat, if the report explicitly states that all subjects received treatment or control conditions as allocated.
Criterion 10	A *between-group* statistical comparison involves statistical comparison of one group with another. Depending on the design of the study, this may involve comparison of two or more treatments, or comparison of treatment with a control condition. The analysis may be a simple comparison of outcomes measured after the treatment was administered, or a comparison of the change in one group with the change in another (when a factorial analysis of variance has been used to analyse the data, the latter is often reported as a group × time interaction). The comparison may be in the form hypothesis testing (which provides a "p" value, describing the probability that the groups differed only by chance) or in the form of an estimate (for example, the mean or median difference, or a difference in proportions, or number needed to treat, or a relative risk or hazard ratio) and its confidence interval.
Criterion 11	A *point measure* is a measure of the size of the treatment effect. The treatment effect may be described as a difference in group outcomes, or as the outcome in (each of) all groups. *Measures of variability* include standard deviations, standard errors, confidence intervals, interquartile ranges (or other quantile ranges), and ranges. Point measures and/or measures of variability may be provided graphically (for example, SDs may be given as error bars in a Figure) as long as it is clear what is being graphed (for example, as long as it is clear whether error bars represent SDs or SEs). Where outcomes are categorical, this criterion is considered to have been met if the number of subjects in each category is given for each group.

Appendix A. Figure 1: PEDro Scale Item Description and Scoring

Appendix B: Supplementary Material for Chapter 2

Appendix B. Table 1: Description and Scoring Rubric for CBS Games

Task Name	Cognitive Domain	Brief Description	Outcome Measure	Literature Informing Task
1. Monkey Ladder (Visuospatial working memory)	Memory	Sets of numbered squares are displayed all at the same time at random locations within an invisible 5x5 grid. After a variable interval, the numbers are removed leaving just the blank squares visible. A tone cues the participant to	Maximum level achieved (Maximum = 25; Minimum =2)	Non-human primate literature [142]
2. Grammatical Reasoning (Verbal Reasoning)	Reasoning	Problems of the form "The square is not encapsulated by the circle" are displayed on the screen and the participant must indicate whether the statement correctly describes a pair of objects displayed in the centre of the screen. In order to achieve maximum points, the	Total score – which increases or decreases by 1 after each trial depending on whether responses are correct. The first trial has four numbers. The maximum level is	Alan Baddeley's 3- minute grammatical reasoning test [143]
3. Double Trouble (Color-Word Re-mapping)	Reasoning	A colored word is displayed at the top of the screen, for example the word RED drawn in blue ink. Participants must indicate which of two colored words at the bottom of the screen describes the color that the word at the top of the screen is drawn in. The color word mappings may be congruent, incongruent, or doubly incongruent, depending on whether or not the color that a given word describes matches	Total score To gain maximum points, the participant must solve as many problems as possible within 90 seconds. The total score increases or decreases by 1 after each trial depending on whether they responded correctly.	More challenging variant of the Stroop test [144]

Task Name	Cognitive Domain	Brief Description	Outcome Measure	Literature Informing Task
4. Odd One Out (Deductive Reasoning)	Reasoning	A 3x3 grid of cells is displayed on the screen. Each cell contains a variable number of copies of a colored shape. The features that make up the objects in each cell (color, shape, number of copies) are related to each other according to a set of rules. The participant must deduce the rules that relate the object features and select the one cell whose contents do not correspond to those	Total correct To gain maximum points, the participant must solve as many problems as possible within 90 seconds. If the response is correct, the total score increases by one point and the next problem is more complex. If the response is incorrect, the total score decreases by 1 point.	Sub-set of problems from the Cattell Culture Fair Intelligence Test [145]
5. Spatial Span Blocks (Spatial Span)	Memory	16 squares are displayed in a 4x4 grid. A sub-set of the squares flash in a random sequence at a rate of 1 flash every 900 ms. Subsequently, the mouse cursor is displayed and a tone cues the participant to repeat the sequence by clicking on the squares in the same order in which they flashed.	Maximum level achieved (Maximum = 16; Minimum = 2)	Corsi Block Trapping Task [146]
6. Rotations (Spatial Rotation)	Concentration	In this variant, 2 grids of colored squares are displayed to either side of the screen with 1 of the grids rotated by a multiple of 90°. When rotated, the grids are either identical or differ by the position of just 1 square. In order to gain maximum points, the participant must indicate whether the grids are identical, solving as many problems as possible within 90 seconds.	Total score If the response is correct, the total score increases by the number of squares in the grid and subsequent trials have more squares. If the response is incorrect the total score decreases by the number of squares in the grid and subsequent trials have fewer squares. The first grids contain 4 colored squares each.	Spatial Rotation tasks are often used for measuring the ability to manipulate objects spatially in mind [147]

Task Name	Cognitive	Brief Description	Outcome Measure	Literature Informing
7. Feature Match	Concentration	Two grids are displayed on the screen, each containing a set of abstract shapes. In half of the trials the grids differ by just one shape. In order to gain maximum points, the participant must indicate whether or not the grid's contents are identical, solving as many problems as possible within 90	Total score If the response is correct, the total score increases by the number of shapes in the grid and the number of shapes in subsequent trials increases. If the response is incorrect, the total score decreases by the number of shapes in the grid and subsequent trials have fewer shapes. The first grids contain two abstract shapes	Classic feature search tasks that have historically been used to measure attentional processing [148]
8. Digit Span	Memory	Participants view a sequence of digits that appear on the screen one after another. Subsequently, they repeat the sequence of numbers by entering them on the keyboard.	Maximum level achieved (Maximum level = 25; Minimum level = 2)	Computerised variant on the verbal working memory component of the WAIS-R intelligence
9. Hampshire Tree Task (Spatial Planning)	Planning	Numbered beads are positioned on a tree shaped frame. The participant repositions the beads so that they are configured in ascending numerical order running from left to right and top to bottom of the tree.	Total score After each trial, the total score is incremented by adding the minimum number of moves required ×2 – the number of moves actually made, thereby rewarding efficient planning.	Based on Tower of London Task [150] – widely used to measure executive function.

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Appendix B. Table 2: Square Stepping Exercise example patterns

i) Beginner Pattern – focused on walking-like movements and simple steps

Start Walk	**2**		**4**		**2**		**4**		**Finish Walk**
		3		**6**		**3**		**6**	
	1		**5**		**1**		**5**		

ii) Intermediate Pattern – incorporates forward, lateral and diagonal movements

	3	**5**	**3**	**5**	**3**	**5**	**3**	**5**	
Start Walk	**1**	**4**	**1**	**4**	**1**	**4**	**1**	**4**	**Finish Walk**
	2	**6**	**2**	**6**	**2**	**6**	**2**	**6**	

iii) Advanced Pattern – a large number of steps per pattern with multiple movement types

Start Walk	**1**	**3**	**7**	**5**	**1**	**3**	**7**	**5**	**Finish Walk**
	4	**2**	**6**	**8**	**4**	**2**	**6**	**8**	

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- Numbers represent consecutive footsteps
- As designed, we will run the SSE in a group format, whereby 5-6 participants will be designated to a specific SSE mat.
- Participants will progress as a group to the next step pattern after 80% of participants can perform the pattern smoothly.
- For any advanced participants, there are mechanisms by which difficulty can be increased within a current pattern (i.e., increasing step speed; avoiding square frames, etc.).

Appendix C: Statistical Analyses for Chapter 2

Correlation Analyses

Correlation between AC and baseline 24-hour ambulatory BP

Correlations

		x24sbpavg.0	x24dbpavg.0	x24sbppk.0	x24dbppk.0	x24map.0	x24hr.0	ac.0
x24sbpavg.0	Pearson Correlation	1	.635**	.869**	.536**	.844**	.047	.217
	Sig. (2-tailed)		.000	.000	.000	.000	.670	.051
	N	85	85	85	85	85	85	82
x24dbpavg.0	Pearson Correlation	.635**	1	.422**	.734**	.859**	.087	.076
	Sig. (2-tailed)	.000		.000	.000	.000	.429	.495
	N	85	85	85	85	85	85	82
x24sbppk.0	Pearson Correlation	.869**	.422**	1	.444**	.740**	-.054	.163
	Sig. (2-tailed)	.000	.000		.000	.000	.622	.145
	N	85	85	85	85	85	85	82
x24dbppk.0	Pearson Correlation	.536**	.734**	.444**	1	.666**	.193	-.017
	Sig. (2-tailed)	.000	.000	.000		.000	.076	.881
	N	85	85	85	85	85	85	82
x24map.0	Pearson Correlation	.844**	.859**	.740**	.666**	1	.053	.157
	Sig. (2-tailed)	.000	.000	.000	.000		.628	.158
	N	85	85	85	85	85	85	82
x24hr.0	Pearson Correlation	.047	.087	-.054	.193	.053	1	-.253*
	Sig. (2-tailed)	.670	.429	.622	.076	.628		.022
	N	85	85	85	85	85	85	82
ac.0	Pearson Correlation	.217	.076	.163	-.017	.157	-.253*	1
	Sig. (2-tailed)	.051	.495	.145	.881	.158	.022	
	N	82	82	82	82	82	82	85

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Correlation between AC and 6-month ambulatory BP

Correlations

		x24sbpavg.1	x24dbpavg.1	x24sbppk.1	x24dbppk.1	x24map.1	x24hr.1	ac.1
x24sbpavg.1	Pearson Correlation	1	.644**	.821**	.304**	.881**	-.016	.098
	Sig. (2-tailed)		.000	.000	.010	.000	.895	.424
	N	71	71	71	71	71	71	69
x24dbpavg.1	Pearson Correlation	.644**	1	.480**	.461**	.898**	.132	.220
	Sig. (2-tailed)	.000		.000	.000	.000	.273	.070
	N	71	71	71	71	71	71	69
x24sbppk.1	Pearson Correlation	.821**	.480**	1	.358**	.697**	-.085	.201
	Sig. (2-tailed)	.000	.000		.002	.000	.481	.097
	N	71	71	71	71	71	71	69
x24dbppk.1	Pearson Correlation	.304**	.461**	.358**	1	.389**	.030	.124
	Sig. (2-tailed)	.010	.000	.002		.001	.806	.312
	N	71	71	71	71	71	71	69
x24map.1	Pearson Correlation	.881**	.898**	.697**	.389**	1	.035	.199
	Sig. (2-tailed)	.000	.000	.000	.001		.772	.102
	N	71	71	71	71	71	71	69
x24hr.1	Pearson Correlation	-.016	.132	-.085	.030	.035	1	-.458**
	Sig. (2-tailed)	.895	.273	.481	.806	.772		.000
	N	71	71	71	71	71	71	69
ac.1	Pearson Correlation	.098	.220	.201	.124	.199	-.458**	1
	Sig. (2-tailed)	.424	.070	.097	.312	.102	.000	
	N	69	69	69	69	69	69	72

**. Correlation is significant at the 0.01 level (2-tailed).

Correlation between baseline AC, Age and BMI

Correlations

		bmi.0	age.0	ac.0
bmi.0	Pearson Correlation	1	-.169	.054
	Sig. (2-tailed)		.114	.621
	N	89	89	85
age.0	Pearson Correlation	-.169	1	-.024
	Sig. (2-tailed)	.114		.825
	N	89	89	85
ac.0	Pearson Correlation	.054	-.024	1
	Sig. (2-tailed)	.621	.825	
	N	85	85	85

Correlation between 6-month AC, and baseline Age and BMI

Correlations

		age.0	bmi.0	ac.1
age.0	Pearson Correlation	1	-.169	-.122
	Sig. (2-tailed)		.114	.307
	N	89	89	72
bmi.0	Pearson Correlation	-.169	1	.243*
	Sig. (2-tailed)	.114		.040
	N	89	89	72
ac.1	Pearson Correlation	-.122	.243*	1
	Sig. (2-tailed)	.307	.040	
	N	72	72	72

*. Correlation is significant at the 0.05 level (2-tailed).

Appendix D. Western Health Sciences Research Ethics Board

Western Research

Research Ethics

Use of Human Participants - Revision Ethics Approval Notice

Principal Investigator: Dr. Robert Petrella
File Number: 102434
Review Level: Delegated
Protocol Title: Aerobic and Cognitive Exercise in Community-Dwelling Older Adults (REB# 18858)
Department & Institution: Schulich School of Medicine and Dentistry\Geriatric Medicine,Western University
Sponsor: Canadian Institutes of Health Research

Ethics Approval Date: October 11, 2013 **Expiry Date:** December 31, 2014
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Revised Western University Protocol	includes July/2013 and Sept/2013 amendment-Received Sept 19, 2013	
Instruments	Phone-FITT (received Sept 19, 2013)	
Instruments	Description of 12 Cognitive tasks from Cambridge Brain Sciences Battery-Received Sept 19, 2013	
Recruitment Items	Poster for Parkwood Cohort-Received Sept 19, 2013	
Recruitment Items	Poster for South Gate Centre Cohort-Received Sept 19, 2013	
Recruitment Items	Telephone Script-Received Sept 19, 2013	
Revised Letter of Information & Consent	Parkwood Cohort	2013/09/03
Revised Letter of Information & Consent	South Gate Centre Cohort	2013/09/03

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

[redacted]

Signature

Ethics Officer to Contact for Further Information

Erika Basile (ebasile@uwo.ca)	Grace Kelly (grace.kelly@uwo.ca)	Vikki Tran (vikki.tran@uwo.ca)

This is an official document. Please retain the original in your files.

[redacted]

Appendix E. Lawson Health Research Institute Ethics Board

LAWSON HEALTH RESEARCH INSTITUTE

FINAL APPROVAL NOTICE

RESEARCH OFFICE REVIEW NO.: R-12-265

PROJECT TITLE: HM2: Healthy Mind, Healthy Mobility - Dual-task Aerobic Exercise for Older Adults with Cognitive Impairment

PRINCIPAL INVESTIGATOR: Dr. Robert Petrella

DATE OF REVIEW BY CRIC: June 12, 2012

Health Sciences REB#: 18858

Please be advised that the above project was reviewed by the Clinical Research Impact Committee and the project:

Was Approved

PLEASE INFORM THE APPROPRIATE NURSING UNITS, LABORATORIES, ETC. BEFORE STARTING THIS PROTOCOL. THE RESEARCH OFFICE NUMBER MUST BE USED WHEN COMMUNICATING WITH THESE AREAS.

Dr. David Hill
V.P. Research
Lawson Health Research Institute

All future correspondence concerning this study should include the Research Office Review Number and should be directed to Sherry Paiva, CRIC Liaison, LHSC, [redacted]

cc: Administration

Appendix F. Protocol Registration (ClinicalTrials.gov PRS)

![ClinicalTrials.gov PRS — Protocol Registration and Results System]

ClinicalTrials.gov PRS DRAFT Receipt (Working Version)
Last Update: 06/10/2015 14:44

Body and Brain Exercise for Older Adults With Memory Complaints

This study is ongoing, but not recruiting participants.

Sponsor:	Lawson Health Research Institute
Collaborators:	Canadian Institutes of Health Research (CIHR)
Information provided by (Responsible Party):	Rob Petrella, Lawson Health Research Institute
ClinicalTrials.gov Identifier:	NCT02136368

Purpose

The purpose of this study is to investigate whether an exercise class with a cognitive (or brain) training component was more effective than a usual combined aerobic and resistance exercise class for older adults with cognitive complaints (such as concerns about changes in memory or thinking skills). It is hypothesized that the group randomized to the exercise class that includes additional brain training will have greater improvements in brain health.

Condition	Intervention	Phase
Cognitive Ability, General	Behavioral: Multimodal exercise Behavioral: Mind-Motor Exercise Behavioral: Balance and range of motion exercises	N/A

Study Type: Interventional
Study Design: Prevention, Parallel Assignment, Single Blind (Outcomes Assessor), Randomized, Efficacy Study
Official Title: A Combined Exercise Program Plus Cognitive Training for Older Adults With Self-reported Cognitive Complaints: The Multimodal, Mind-motor (M4) Study

Further study details as provided by Rob Petrella, Lawson Health Research Institute:

Primary Outcome Measure:

- Composite score from Cambridge Brain Sciences Cognitive Battery - 12 tasks [Time Frame: 6 months] [Designated as safety issue: No]
  To assess global cognitive function

Secondary Outcome Measures:

- Composite score from Cambridge Brain Sciences Cognitive Battery - 12 tasks [Time Frame: 12 months] [Designated as safety issue: No]
  To assess global cognitive function
- Gait variability (stride time) under dual-task conditions [Time Frame: 6 & 12 months] [Designated as safety issue: No]
  Gait variability is the stride-to-stride fluctuations of the way someone walks and will be calculated as the coefficient of variation of step length (SD/mean x100). Measured with GAITRite system.

- Gait variability (stride time) under single-task conditions [Time Frame: 6 & 12 months] [Designated as safety issue: No]
  Gait variability is the stride-to-stride fluctuations of the way someone walks and will be calculated as the coefficient of variation of step length (SD/mean x100). Measured with GAITRite system.
- Gait velocity (speed) under dual-task conditions [Time Frame: 6 & 12 months] [Designated as safety issue: No]
  Average walking speed (gait velocity) measured with the GAITRite system
- Gait velocity (speed) under single-task conditions [Time Frame: 6 & 12 months] [Designated as safety issue: No]
  Average walking speed (gait velocity) measured with the GAITRite system
- Step length (average) under dual-task conditions [Time Frame: 6 & 12 months] [Designated as safety issue: No]
  Mean step length calculated from GAITRite system
- Step length (average) under single-task conditions [Time Frame: 6 & 12 months] [Designated as safety issue: No]
  Mean step length calculated from GAITRite system
- Carotid Artery Compliance [Time Frame: 6 & 12 months] [Designated as safety issue: No]
  Measured from non-invasive vascular assessment with B-mode Ultrasound over the carotid artery (in the neck).
- Carotid Artery Intima-media thickness [Time Frame: 6 & 12 months] [Designated as safety issue: No]
  Measured from non-invasive vascular assessment with B-mode Ultrasound over the carotid artery (in the neck).
- Ambulatory Systolic Blood Pressure [Time Frame: 6 & 12 months] [Designated as safety issue: No]
  Average systolic blood pressure over a 24 hour time period.
- Clinic Systolic Blood Pressure [Time Frame: 6 & 12 months] [Designated as safety issue: No]
  Average systolic blood pressure from in clinic final 2 (out of 3) readings
- Ambulatory Diastolic Blood Pressure [Time Frame: 6 & 12 months] [Designated as safety issue: No]
  Average diastolic blood pressure over a 24 hour time period.
- Clinic Diastolic Blood Pressure [Time Frame: 6 & 12 months] [Designated as safety issue: No]
  Average diastolic blood pressure from in clinic final 2 (out of 3) readings
- Composite score of memory tasks from Cambridge Brain Sciences Cognitive Battery [Time Frame: 6 & 12 months] [Designated as safety issue: No]
- Composite score of executive function tasks from Cambridge Brain Sciences Cognitive Battery [Time Frame: 6 & 12 months] [Designated as safety issue: No]
- Composite score of concentration tasks from Cambridge Brain Sciences Cognitive Battery [Time Frame: 6 & 12 months] [Designated as safety issue: No]
- Total balance score [Time Frame: 6 & 12 months] [Designated as safety issue: No]
  Total score calculated from the the Fullerton Advanced Balance scale

Other Pre-specified Outcome Measures:
- Prosaccade reaction time in response to flash of light [Time Frame: 6 months] [Designated as safety issue: No]
  The reaction time of the eye when instructed to look toward a flash of light.
- Change in blood flow to the pre-frontal cortex in response to a randomly selected cognitive task. [Time Frame: 6 months] [Designated as safety issue: No]
  Neuroimaging assessment with functional magnetic resonance imaging
- Antisaccade reaction time in response to flash of light. [Time Frame: 6 months] [Designated as safety issue: No]
  The reaction time of the eye when instructed to look away from a flash of light.
- Change in blood flow to the parietal cortex in response to a randomly selected cognitive task. [Time Frame: 6 months] [Designated as safety issue: No]
  Neuroimaging assessment with functional magnetic resonance imaging

Estimated Enrollment: 140
Study Start Date: January 2014
Estimated Primary Completion Date: October 2015
Estimated Study Completion Date: April 2016

Arms	Assigned Interventions
Experimental: Multi-Modal, Mind Motor Exercise (M4) Attend 60 minute exercise class three times per week for 24 weeks. Exercise class includes 45 minutes of multimodal exercise and 15 minutes of mind-motor exercise.	Behavioral: Multimodal exercise Community-based group exercise classes following Canadian Centre for Activity and Aging exercise guidelines. Exercise classes consist of 5 min warm-up, 20 min aerobic exercise, 5 min aerobic cool-down, 10 min full-body resistance exercise, 5 min stretching (total 45 min) Other Names: Exercise intervention Behavioral: Mind-Motor Exercise Square Step Exercise involves mimicking a stepping pattern demonstrated by an instructor. The stepping patterns become progressively difficult and involve forward, backward, lateral and diagonal movements on a 250cm long mat with 25cm square grids (15 min). Other Names: Square Stepping Exercise
Active Comparator: Multi-Modal Exercise (M2) Attend 60 minute exercise class three times per week for 24 weeks. Exercise class includes 45 minutes of multimodal exercise and 15 minutes of balance and range of motion exercises.	Behavioral: Multimodal exercise Community-based group exercise classes following Canadian Centre for Activity and Aging exercise guidelines. Exercise classes consist of 5 min warm-up, 20 min aerobic exercise, 5 min aerobic cool-down, 10 min full-body resistance exercise, 5 min stretching (total 45 min) Other Names: Exercise intervention Behavioral: Balance and range of motion exercises Community-based group exercise designed to improve balance and range of motion of the joints (15 min)

Detailed Description:

Older adults with self-reported cognitive complaints (CCs) may be at increased risk for the development of Alzheimer's disease and dementia. Cognitive decline in older adults, particularly reduced memory and executive function is associated with functional decline, institutionalization, and increased health care costs. Similarly, cardiovascular risk factors have been associated with cognitive and functional impairment in aging. Aerobic exercise has been shown to improve vascular function and blood flow in the brain's prefrontal cortex. In turn, resistance training can produce functional changes within distinct cortical regions during the encoding and recall of association tasks and has been shown to increase circulating neural growth factors (i.e., a proposed mechanism by which cognition may be preserved or improved in old age). Recent evidence also suggests that cognitive training may improve the cognitive performance of older adults.

Therefore, we will investigate the impact of a combined exercise program (multimodality exercise; M2) compared to a combined exercise program with a cognitive component (multimodality, mind-motor exercise; M4) on cognition, cognitive-motor, mobility, neural functioning and vascular outcomes in older adults with cognitive complaints. Community-based exercise programs for older adults provide widespread access, are relatively inexpensive, and provide opportunities for social interaction.

The primary purpose of this study is to compare the effects of the M2 and M4 exercise programs on brain health. This study will also examine the effects of the different exercise programs on cardiovascular risk factors and mobility. In a subset of participants, cognitive-motor and neural functioning outcomes will be examined.

Eligibility

Ages Eligible for Study: 55 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: Yes

Criteria
Inclusion Criteria:

- aged 55 years or older
- self-reported cognitive complaint (defined as answering yes to the question "Do you feel like your memory or thinking skills have gotten worse recently?").
- independent on instrumental activities of daily living

Exclusion Criteria:

- Probable Dementia (i.e., diagnosis OR Mini-Mental State Examination score <24)
- Other neurological conditions or major psychiatric disorders (i.e., Parkinson's disease; bipolar disorder)
- Previous history of severe cardiovascular conditions (i.e., myocardial infarction or stroke < 1-year ago; end stage congestive heart failure; end stage renal disease)
- Severe sensory impairment (i.e., blind)
- Significant orthopedic conditions (i.e., severe osteoarthritis)
- Clinical depression (determined via >=16 on the Center for Epidemiologic Studies - Depression Scale AND review by primary study physician)
- Have blood pressure >180/100 mmHg or <100/60 mmHg
- Unable to comprehend questionnaire material
- Any other factors that could potentially limit ability to fully participate in the intervention

Contacts and Locations

Locations
Canada, Ontario
Gymnasium
Woodstock, Ontario, Canada, N4V 0B1

Investigators

Principal Investigator:	Robert J Petrella, MD, PhD	The University of Western Ontario

More Information

Responsible Party:	Rob Petrella, Principal Investigator, Lawson Health Research Institute
Study ID Numbers:	M4W 18858
Health Authority:	Canada: Institutional Review Board

Curriculum Vitae

Amanda Deosaran

Graduate Research Assistant
Aging, Rehabilitation, & Geriatric Care Centre (ARGC)
St. Joseph's Parkwood Hospital
London, Ontario
Canada

CURRENT POSITION

Masters (MSc), Kinesiology

London ,ON

Faculty of Health Sciences, University of Western Ontario

Sept. 2013 - Current

Thesis title: "The effects of a multiple modality-modality mind-motor (M4) program on vascular outcomes in community-dwelling older adults with subjective cognitive complaints"

Thesis committee: Dawn P. Gill, Cheri L. McGowan, Robert J. Petrella (advisor)

EDUCATION

Bachelors of Science (B.Sc.) Honours, Biological Sciences (BIOS)

Guelph, ON

College of Biological Sciences, University of Guelph

Apr. 2013

Undergrad thesis title: "Separate Effects of Self-Control Depletion and Mood on Risk Taking"

Thesis Supervisor: Dr. Harvey Marmurek

RESEARCH EXPERIENCE

Graduate Research Assistant

London, ON

Aging, Rehabilitation & Geriatric Care Research Centre (ARGC), Parkwood Hospital

Sept. 2013 – Aug. 2015

Supervisor: Dr. Robert Petrella

Principle Investigator, The effects of self-control depletion and mood on risk taking in first year University of Guelph students

Guelph, ON

Department of Psychology, University of Guelph

Sept. 2012 – Dec 2012

Principle Investigator: Amanda Deosaran (with Dr. Harvey Marmurek and Brian Douglas)

Undergraduate Research Assistant, Assessing whether gender and personality traits are predictors of risk taking in University of Guelph students

Guelph, ON

Department of Psychology, University of Guelph

Jan. 2013 – Apr. 2013

Supervisor: Dr. Harvey Marmurek

Principle Co-Investigator, Develop innovative uses/marking strategies for Ontario soybeans such as extracting isoflavones to develop a tea as an alternative to hormone therapy and supplements for menopausal women

Guelph, ON

Project Soy: Soybean Opportunities for Youth

Jan. 2012 – Mar. 2012

Department of Food Science, University of Guelph

Principle Investigator: Amanda Deosaran (with Manvir Hundal, Steven Persaud, and Anu Stanley)

SCHOLARSHIPS, AWARDS, & DISTINCTIONS

1. **Travel Grant ($500)**, Faculty of Health Sciences (2014)
2. **Western Graduate Scholarship ($10,000)**, University of Western Ontario (2013-2015)
3. **Dean's Honors List,** University of Guelph (2012-2013)

PROFESSIONAL SERVICES & AFFILIATIONS

<u>Professional Memberships</u>

- American College of Sports Medicine (ACSM) Student Member

Mar. 2014 – Apr. 2015

Professional Services

- Volunteer Mentor, Family and Children Services of Kitchener-Waterloo

Feb. 2013 – present

- Registration Volunteer, Parkinson's Society Annual Walk

Aug. 2012 – Sept. 2012

-Children's Outpatient Volunteer, Grand River (main) Hospital

Sept. 2011 – Apr. 2012

- Dialysis Volunteer, Grand River (main) Hospital

June 2011 – Sept. 2011

- Health and Rehabilitation Volunteer, Freeport Hospital

May 2010 – May 2011

TEACHING EXPERIENCE

- Graduate Teaching Assistant (Introduction to Exercise Physiology), Department of Kinesiology, Western University (Sept. 2013 – Dec. 2013)
- Tutor for English as a Second Language (ESL), Kitchener-Waterloo Multicultural Centre (June 2010 – Sept. 2010)

SUPERVISORY & MENTOR EXPERIENCE

- University of Guelph Department of Psychology Undergraduate Volunteers – Supervisor (in conjunction with Dr. Harvey Marmurek) on all aspects of their work on assessing gender, personality and risk taking in the Psychology Research Lab
    - Allie Ali (Sept. 2012 – Dec. 2012); Anthony Natale (Jan. 2013 – Apr. 2013); Alex Veitch (Jan. 2013 – Apr. 2013)

RESEARCH FUNDING - SUBMITTED

Combined Aerobic Exercise and Cognitive Training in Older Adults with Self-Reported Cognitive Complaints: The Multi-Modal, Mind-Motor (M4) Study

Operating Grant: 2013-2014 (CIHR Open Operating Grant – Spring 2014 Competition)

Canadian Institutes of Health Research

Principal Investigator: Robert J. Petrella

Role: Research Assistant

$628,860 CAD total (Oct. 2014 – Sept. 2017)

BIBLIOGRAPHY

Refereed Poster Presentations (2 Total; Presenting author is underlined)

1. **Amanda Deosaran**, Dawn P. Gill, Michael A. Gregory, Noah Koblinsky, Heather Morton, Ashleigh De Cruz, Lee Gonzalez, Clara Fitzgerald, Ryosuke Shigematsu, Robert J. Petrella. Effects of combined aerobic exercise and dual-task training on vascular health in older adults.
   FHS-ARGC Symposium at Western University. Feb. 7th, 2014.

2. **Amanda Deosaran**, Dawn P. Gill, Michael A. Gregory, Noah Koblinsky, Heather Morton, Ashleigh De Cruz, Lee Gonzalez, Clara Fitzgerald, Ryosuke Shigematsu, Robert J. Petrella. Effects of combined aerobic exercise and dual-task training on vascular health in older adults. American College of Sports Medicine's (ACSM) 61st Annual Meeting, 5th World Congress on Exercise is Medicine®, Orlando, FL, May 25-30, 2014. Published in Med Sci Sports Exercise 2014, 46;(5 Suppl).